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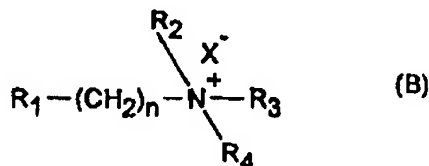
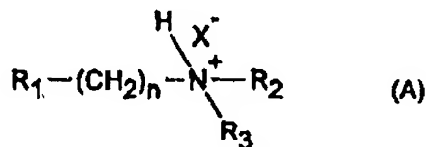
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(54) Title: **USEFUL FORMULATIONS OF ACID ADDITION SALT DRUGS**

(57) Abstract

Methods of and formulations for administering acid addition salts of compounds of Formula (A) or Formula (B), wherein R₁ comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R₂, R₃ and R₄ are alkyl or aryl groups, and X⁻ is an anion. In the methods, a sterile injectable formulation of a liquid vehicle containing the acid addition salt in solution is adjusted in pH for reducing the development of undesirable side effects of the material or provided at a pH within a range of about 5.5 to 7.0, and administering these acid addition salts by intramuscular injection contain the salt at a concentration of at least about 50 mg/ml and are at a pH within a range of about 5.5 to 7.0.



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USEFUL FORMULATIONS OF ACID ADDITION SALT DRUGS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending U.S. patent application Serial No. 08/479,113 filed June 7, 1995, which is a division of copending U.S. patent application Serial No. 08/218,072 filed March 25, 1994. The disclosures of both of these patent applications are incorporated herein by this reference.

BACKGROUND OF THE INVENTION

This invention relates to acid addition salt drugs having utility in the treatment of human patients. More particularly it relates to new and improved formulations and methods of administration of such acid addition salt drugs.

Nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics represent a wide range of diverse chemical and pharmacological structures, but they share a common property of modifying the tumor response to radiation or chemotherapy. A variety of chemical structures including the nitroimidazoles, phenothiazines, butyrophenones, halopyrimidines, benzamides and nicotinamides are known to possess radio- and chemosensitizing properties (Horsman et al, *Acta Oncologica* 34:571-587, 1995; Brown et al, *Cancer Treatment Symposia* 1, 85-101, 1984, Pu et al, *Oncology* 9(8):707-721, 1995, George and Singh, *Indian J. Expt. Biol.* 22:305-307, 1984, Kennedy et al, *Int. J.*

Radiat. Oncol. Biol. Phys. 12:1367-1370, 1986). These various classes of agents are believed to accomplish this mechanistic action either by altering tumor blood supply to overcome hypoxia, inhibiting DNA repair, imbalancing calcium homeostasis or combinations thereof (Horsman et al, Acta Oncologica 34:571-587, 1995, Hirst et al, Br. J. Cancer 67:1-6, 1993, Wood and Hirst, J. Radiat. Oncol. Biol. Phys. 16:1141-1144, 1989; Menke and Vaupel, Radiation Res. 114:64-76, 1988; Rosenthal and Hait, Yale J. Biol. Med. 61: 39-49, 1988, Lybak and Pero, Carcinogenesis 12: 1613-1617, 1991, Olsson et al, Carcinogenesis 16: 1029-1035, 1995; Olsson, et al, Br. J. Cancer, In Press, 1996).

Regardless of the precise mechanism(s) the ultimate result is accumulation of DNA damage and an increase in tumor cytotoxicity either by necrosis or apoptosis (Kerr and Winterford, Cancer 73:2013-2026, 1993). As a result, these agents are all potential cancer therapy drugs even though they may have other well defined clinical uses. For example, metoclopramide, an N-substituted benzamide, has been used as an antiemetic for over 30 years (Harrington et al, Drugs 25: 451-494, 1983) but recently it has been shown to be an effective radio- and chemo-sensitizer (Pero et al, Biochimie 77:385-391, 1995, Kjellén et al, Eur. J. Cancer 31A(13/ 14):2196-2202, 1995). Furthermore, most drugs having well established clinical uses are known to mediate their effects by antagonizing high affinity receptors capable of initiating physiological responses relating to many disease processes. Conformation and charge of these chemical structures, in turn, determine their abilities to antagonize receptors and mediate drug related efficacious responses.

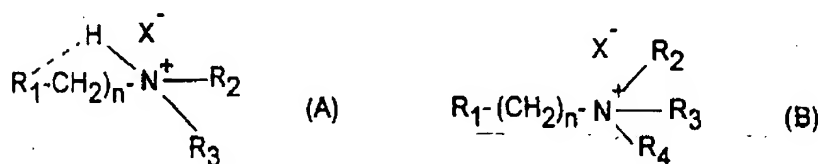
SUMMARY OF THE INVENTION

Reference is made hereinbelow to the following four papers, in all of which applicant herein is a co-author: (1) R.W. Pero, M. Simanaitis, A. Olsson, A. Amiri and I. Andersen, "Pharmacokinetics, Toxicity, Side Effects, Receptor Affinities and In Vitro Radiosensitizing Effects of the Novel Metoclopramide Formulations, Sensamide and Neu-Sensamide," unpublished typescript, 1996, pp. 1-25 + 5 Figures (hereinafter "Pero et al unpublished 1996"), now published as Pharmacology & Toxicology 80:231-239, 1997 (2) A. Amiri, A.R. Olsson, J. Hua and R.W. Pero, "Apoptosis in HL-60 Cells As A Model for Determining Sensitization of Radio- And Chemotherapies By N-Substituted Benzamides," unpublished typescript, 1996, 14 pp. (unpaginated) + 6 Figures (hereinafter "Amiri et al unpublished 1996"), (3) H.H. Rotmensch, G.P. Mould, J.A. Sutton, S. Kilminster, C. Moller, R.W. Pero, "Comparative Central Nervous System Effects and Pharmacokinetics of Neu-Sensamide and Metoclopramide in Healthy Volunteers," unpublished typescript, 1996, pp. 1-19 + 2 Figures (hereinafter "Rotmensch et al unpublished 1996"), now published as J. Clin Pharmacol 37:222-228 (1997), (4) A. Schwartz and R.W. Pero, "Evidence for Conformational Mobility of Metoclopramide as a Function of pH: Implications for Drug Design," unpublished typescript, 1996, 18 pp. (unpaginated) (hereinafter "Schwartz et al unpublished 1996").

One of the most popular chemical functionalities (i.e. structures, substitutions) used in drug design is a tertiary or a quaternary nitrogen usually introduced via an alkylaminodialkyl side chain, so that drugs such as the nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics

could be converted to more water soluble formulations for clinical administration. However, drug formulation research with the N-substituted benzamides (incident to the development of the present invention) has so far shown that this structure can dramatically alter the pharmacological properties of, for example, metoclopramide simply by changing the pH of the formulation. Molecular modeling experiments support that Neu-Sensamide™ ("neutral" metoclopramide) has been formulated without the presence of a hydrogen mediated-bond between the tertiary ammonium ion and the carboxamide oxygen atom, whereas this hydrogen mediated-bond is present in Sensamide™ ("acidic" metoclopramide) (Schwartz et al unpublished 1996). Neu-Sensamide™ has a reduced extrapyramidal side effect profile in rats and humans but the radiosensitizing properties remain unaltered compared to Sensamide™ at equimolar doses (Amiri et al unpublished 1996; Hua et al, Anti-Cancer Drugs 6:451-453, 1995; Pero et al, Biochimie 77:385-393, 1995; Pero et al unpublished 1996; Rotmensch et al unpublished 1996). Therefore, it is logical to extrapolate these data to other drugs containing acid addition salt structures in the following way:

Compounds that can form acid salts of types A or B:



R_{1-4} = alkyl or aryl groups; X^- = any anion, normally Cl^- or Br^- or I^-

(1) A tertiary nitrogen is present that can form an acid addition salt (Type A) or a quarternary ammonium ion is present (Type B) and/or

(2) R_1 comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with the tertiary/quarternary nitrogen, e.g. a carbonyl or carboxylic oxygen atom.

Have the potential to become pharmacologically altered because:

(1) Most drugs express their biological activity by binding receptors.

(2) Receptor affinities are determined by conformation and charge-distribution of the ligand drugs.

(3) Altering the pH of acid addition salt drugs can alter their receptor affinity by either conformation or charge-distribution or both.

(4) Altering receptor affinity as has been accomplished with Sensamide™/Neu-Sensamide™ does not alter radiosensitizing potency (Hua et al, Anti Cancer Drugs 6:451-453, 1995; Pero et al unpublished 1996).

There are at least 143 clinically available drugs (listed in Table 2 below) having potential properties of radiosensitization, and altering their receptor affinities by pH adjusting their formulations that in turn contain acid addition salt

substitutions, could affect side effect profiles permitting higher doses to be used for radiosensitization or other pharmacological indications. This point is a novel discovery not obvious as previously known in the literature. Although the 143 clinically available drugs have been the subject of many patents and patent applications, including recent patents and applications concerned with the radio-chemo-sensitizing and antiemetic properties of N-substituted aryl compounds such as the benzamides and nicotinamides (U.S. provisional Patent Application No. 60/013,072, U.S. Patent No. 4,576,386, U.S. Patent No. 5,340,565, U.S. Patent No. 5,215,738, U.S. Patent No. 5,032,617 and U.S. Patent No. 5,041,653), the latter citations do not disclose that the pH of acid addition salt drugs could alter chemical structure, and in turn change the pharmacological properties of the formulations. Examples of compounds that are not as yet clinically available but that are capable of forming acid addition salts with a potential for alteration of pharmacological properties by pH adjustment are 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-(2,3-b) guinoxline (procedures for synthesizing 3-chloro procainamide and N-(2-diethylamino-ethyl) nicotinamide are described in copending U.S. provisional patent application No. 60/013,072, filed March 8, 1996, the disclosure of which is incorporated herein by this reference). Hence in a broad sense this invention is not confined to the 143 clinically available drugs listed in Table 2, but embraces the use of all compounds formulated to possess water solubility by formation of a substituted amide acid addition salt structure. The aforementioned U.S. Patent Application Serial No. 08/218,072 discloses that metoclopramide, a N-substituted benzamide, can undergo pH-sensitive conformational changes. However, the claims of this application and its division, Serial No. 08/479,113, are respectively directed to

the N-substituted benzamides and phenothiazines and do not include claims covering other acid addition salt drugs.

The present invention, in a first aspect, contemplates the provision of a method of administering to a human patient material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, comprising the steps of providing a sterile injectable formulation comprising a liquid vehicle containing the material in solution and injecting the formulation into the patient in an amount for delivering to the patient a dose of about one to about 100 mg/kg of the material. In important embodiments of this method, the injection is intramuscular, also, conveniently or preferably, the material to be administered is in the acid addition salt form, pH adjusted to 5.5 - 7.0.

Intramuscular injection, to achieve a dose of 1 - 100 mg/kg, requires a much more concentrated formulation than i.v. injection of a like dose, owing to the limited tolerance of muscle tissue for injected fluid. Whereas a solution at a 5 mg/ml concentration of metoclopramide hydrochloride is suitable for i.v. injection of a dose of 5 mg/kg, a concentration of at least about 50 mg/ml or even more (preferably, in many cases, as much as 100 mg/ml) is needed to administer a like dose by intramuscular injection. At these high concentrations, present-day commercial acid addition salt formulations tend to produce local tissue toxic reactions at the injectable site if not pH adjusted to 5.5 - 7.0 (U.S. Patent application No. 08/218,072, Pero et al unpublished 1996).

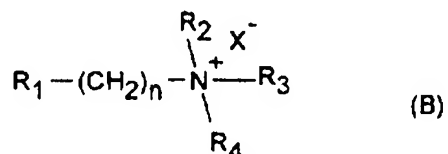
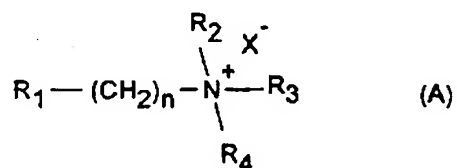
Further in accordance with the invention, a concentrated acid addition salt formulation (e.g. 100 - 7000 mg/ml) is advantageously provided at a pH of about 5.5 to 7.0, for intramuscular injection. At pH values within this range (which is substantially higher, i.e. less acidic, than the pH of currently available formulations of equivalent concentration), local tissue toxic reactions are satisfactorily minimized or avoided, yet without adversely affecting the solubility of acid addition salt drugs or their therapeutic activity. A pH above 7.0 would derogate from solubility, while values below about 5.5 are insufficient to achieve the desired reduction in local tissue side effects. It has been shown that this is the case because an acid addition salt formulation of metoclopramide at pH 2.5 - 3.5 caused local tissue irritation but when neutralized to pH 6.5 - 7.0 a substantially reduced local tissue reaction was observed (U.S. Patent application No. 08/218,072, Pero et al unpublished 1996).

In a second aspect, the invention contemplates the provision of a sterile injectable formulation for intramuscular administration to a human patient, comprising a material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, a liquid vehicle in which the material is in solution being present in the formulation in a concentration of at least about 50 mg/ml; and the formulation being at a pH within a range of about 5.5 to 7.0. In these formulations, the solution pH, once established, may be stabilized to a less variable range (e.g. <0.5 pH unit) by the inclusion of a phosphate or other buffer, or alternatively, by the inclusion of a preservative such as sodium metabisulfite to prevent auto-oxidation.

Also surprisingly, it has been found that the administration of an acid addition salt, metoclopramide hydrochloride, in otherwise conventional formulations (which contain Na^+ ions, present in the saline solution and/or introduced as sodium metabisulfite) but at a pH of about 5.5 to 7.0 substantially prevents the extrapyramidal side effects of known metoclopramide treatments (Pero et al, Biochimie 77:385-393, 1995, Pero et al unpublished 1996). In a third aspect, which is not limited to intramuscular injection, the invention contemplates the provision of a method of administering to a human patient material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, comprising a liquid vehicle containing the material in solution (and, in some instances, also containing Na^+ ions), adjusting the pH of the formulation for reducing the development of undesirable side effects or improving pharmacological indications of the material, and administering the formulation having the adjusted pH to the patient. A preferred or effective range of formulation pH for reduction or avoidance of extrapyramidal side effects is between about 5.5 and 7.0.

Stated in some respects more broadly, the invention in each of the above described aspects may be embodied in a method or formulation wherein the aforementioned material is selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of

Formula (B) having a quaternary ammonium ion present, and mixtures thereof, Formula (A) and Formula (B) being as follows:



wherein R_1 comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with the tertiary nitrogen of Formula (A) or the quaternary ammonium ion of Formula (B), R_2 and R_3 and R_4 are alkyl or aryl groups, and X^- is an anion. In specific embodiments, the hydrogen bond acceptor site is a carbonyl or carboxylic oxygen atom, and X^- is Cl^- , F^- , Br^- or I^- . Advantageously or preferably, the material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A) or Formula (B), and mixtures thereof.

Further features and advantages of the invention will be apparent from the detailed description herein below set forth, together with the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a graph on which the UV absorption intensity is plotted against wavelength of UV absorption between 195 nm and 215 nm for 100 μ M solutions of metoclopramide pH adjusted between 4.8 and 6.0 with 1 N HCl or 1 N NaOH.

Fig. 2A is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) and acidic (pH 2-3) 3-chloroprocainamide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2B is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) and acidic (pH 2-3) lidocaine are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2C is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) and acidic (pH 2-3) metoclopramide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2D is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) and acidic (pH 2-3) remoxipride are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2E is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) and acidic (pH 2-3) procainamide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2F is a graph on which the UV absorption intensity of 100 μ M solutions of aqueous (pH 5-6) chlorpromazine are plotted against the wavelength UV absorption between 195 nm and 380 nm.

Fig. 2G is a graph on which the UV absorption intensity of 100 μ M solutions of acidic (pH 2-3) chlorpromazine are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

DETAILED DESCRIPTION

The invention is embodied in methods involving the use of pH adjustment of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, to reduce the development of undesirable side effects of the drug without affecting or enhancing the pharmacological properties such as antiemetics, antiarrhythmics, antidepressants, antipsychotics, antihypertensives, adrenergics, anaesthetics, or the enhancement of radio- and chemotherapies of cancer.

In addition, the invention is embodied in methods involving the use of preparing aqueous sterile injectable formulations of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, with pH adjustment, in order to avoid undesirable side effects of the drug without affecting or improving the indicated clinically useful

pharmacological properties (e.g. enhancement of radio- and chemo-therapies of cancer).

In another aspect, the practice of this invention involves consideration of the pH of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below. The 1993 Physicians' Desk Reference lists over 145 hydrochloride salt formulations as available for clinical use. Most of these hydrochloride salt formulations are acidic solutions ranging in pH from 2 to 6.5 depending on the initial drug concentration and formulation ingredients (American Society of Hospital Pharmacists, 1993, Sveriges Läkersmedels Information AB, FASS, 1993). In order to deliver doses of 1-100 mg/kg by intramuscular injection to patients, the injectable formulations would require initial drug concentrations of around 100 to 7000 mg/ml, which in most cases is a concentration having a pH range of 1 to 4.5 depending on its formulation (American Society of Hospital Pharmacists, 1993, FASS, 1993). Because commercial preparations of solutions of acid addition salt drugs drastically vary in pH, and because they can be pH adjusted from 2 to 6.5 without regulatory restrictions, the prior art teaches that there is no difference in biological activity associated with changes in pH between 2 and 6.5. However, applicant herein has found that when acidic formulations of metoclopramide hydrochloride solutions within a pH range of 2 to 3.7 are compared to a neutralized formulation at around pH 7.0, the local tissue toxic reaction at the site of intra-muscular injection and the extrapyramidal side effect of sedation, are substantially reduced when the neutralized formulation is administered (Pero et al, Biochimie 77:385-393, 1995; Pero et al unpublished 1996). Hence, this

invention embraces the feature that high concentrations of metoclopramide hydrochloride (e.g. 100 mg/ml), and by analogy other acid addition salt drugs because the drug itself is acidic, which would be required for intramuscular administration of metoclopramide or other acid addition salt drugs as pharmacological agents, have fewer toxic side effects in the near neutral pH range than in the acidic form, which in turn are currently the clinically available forms of these drugs.

Metoclopramide and the other acid addition salt drugs listed in Table 2 below are known to bind to high affinity receptors such as both the dopamine₂ (D₂) receptor and the 5-hydroxytryptamine₃ (5-HT₃) receptor (Pharmacokinetic principles in the use drugs, in Medical Pharmacology, A. Goth ed., C.V. Mosby Company, tenth edition, St. Louis, MO, pages 15-30, 1981; Harrington et al, Drugs 25:451-494, 1983, Blower, Eur. J. Cancer 26 (Suppl. 1): S8-S11, 1990). The side effects of acid addition salt drugs are believed to be delivered from receptor binding; for example, extrapyramidal side effects generated from D₂ binding (King and Sanger, Drugs of the Future 14(9):875-889, 1989). These data from the scientific literature support and are consistent with the altered systemic biological effects of acidic metoclopramide hydrochloride salt formulations described herein (Pero et al unpublished 1996). As already mentioned above, acidic metoclopramide has a conformation altering pH sensitive hydrogen mediated-bond which is lacking in neutralized metoclopramide (Pero et al, Biochimie 77:385-393, 1995; Schwartz et al unpublished 1996). This finding is supported by the data revealed in Examples 1-3 which establish that a wide variety of drugs containing tertiary nitrogen substitutions that can convert drugs to acid addition salts, have very similar UV spectra changes indicative of the pH

sensitive conformational changes observed for metoclopramide especially at A_{200} (wavelength of 200 nm). In addition, it would have been an unexpected observation for one skilled in the art to have been able to predict that metoclopramide or other acid addition salt drugs could form a chemical interaction (e.g. a hydrogen bond) stable enough to be transported from the site of intramuscular injection to receptors in the brain in order to mediate an enhanced efficacy or side effect (e.g. sedation).

The UV spectra of the Examples below were run using a Beckman scanning UV-visible spectrophotometer with a quartz cell having a 1 cm path length. The spectra were produced by scanning the UV absorption produced between 195 nm and 380 nm (379 nm in Fig. 1) at a bandwidth of 5 nm. 100 μ M samples of the drugs or model compounds were acidified to pH 2-3 and their UV spectra were recorded. These UV spectra were compared with the UV spectra determined at ambient (aqueous) pH which was normally between pH 5 and 6. In some cases the ambient drug solutions were titrated with 1N HCl and 1N NaOH to produce pH gradient solutions which were then subjected to scanning of the UV spectrum between A_{195} and A_{380} . The UV spectra were corrected for absorption from appropriate solvent blanks.

Example I

UV spectral evidence for the pH sensitive conformation change in metoclopramide.

There is considerable analytical evidence supporting that a hydrogen bond is formed in acidic aqueous solutions of metoclopramide between the tertiary nitrogen of the N-ethylaminodiethyl substitution and the carbonyl of the carboxamide group of substituted benzamide (Reviewed by Schwanz et al unpublished 1996). The data in Fig. 1 report the result of a detailed UV spectral analysis of metoclopramide solutions carefully adjusted in pH between 4.8 and 6.0. The UV absorption spectra recorded between 195 nm and 215 nm show a very sharp change in maximal absorption in metoclopramide solutions around pH 5.0. These UV spectra changes around 5.0 were taken as strong supportive evidence for the shifting of equilibrium between the two conformational forms of metoclopramide, namely, one with the pH sensitive hydrogen bond present and one without it. Because acidic metoclopramide induces extrapyramidal side effects whereas neutral metoclopramide does not (Pero et al, *Biochimie* 77:385-393, 1995, Pero et al unpublished 1996, Rotmensch et al unpublished 1996), Fig. 1 also clarifies that unpredictable but detectable pH sensitive UV absorption spectral changes reflect conformational structural changes in metoclopramide altering the receptor mediated side effects of this drug.

Example 2

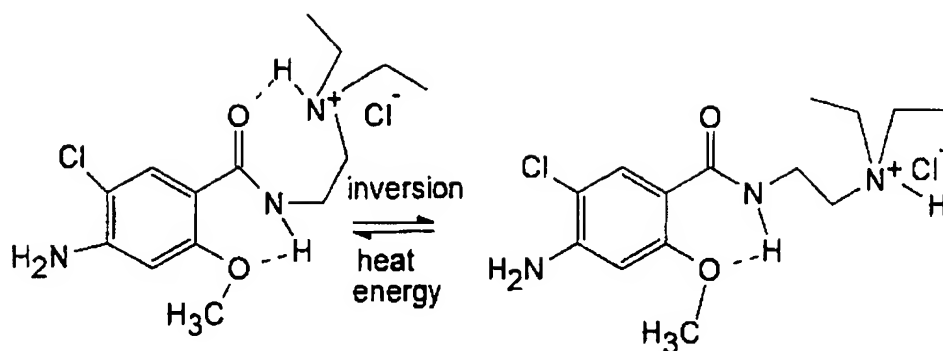
UV spectral evidence for pH sensitive changes of drugs having alkylaminodialkyl substitutions that are capable of forming acid addition salts.

First, the data in Figs. 2A-2G show that drugs that contain alkylaminodialkyl substitutions can have very different UV absorption maxima in aqueous solution, and several areas of each of these UV absorption maxima can be shifted and varied in intensity due to acidic pH adjustment into the range pH 2. Second, the most striking change in UV absorption was associated with pH adjustment at A_{200} for all the drugs containing alkylaminodialkyl substitutions.

Example 3

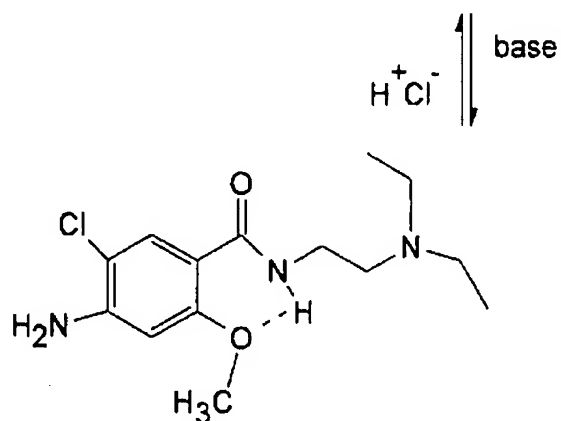
UV spectral evidence indicating alterations in A_{200} resulting from proposed pH sensitive conformational changes in the structure of N-alkylaminodialkyl substituted drugs.

The data in Table 1 show that aryl N-alkylaminodialkyl substitutions contribute mainly to the pH adjusted UV spectra in the 200 nm range. This UV region has been identified as being of interest by comparison to the UV spectral changes associated with pH adjustment of metoclopramide aqueous solutions (presented in Example 1). Molecular modeling, analytical chemical analyses, extrapyramidal biologic responses and the previous scientific literature have confirmed the existence of a hydrogen mediated-bond between the carbonyl of the carboxamide and the tertiary nitrogen present in the N-ethylaminodiethyl substituted benzamide ring of metoclopramide (Schwartz et al unpublished 1996; Pero et al, Biochimie 77: 385-393 1995). Hence, acidic metoclopramide has the conformational change imposed by the presence of this pH sensitive hydrogen mediated-bond whereas neutral metoclopramide has an extended conformation due to the lack of this hydrogen bond. The pH dependence of intramolecular hydrogen bonding in metoclopramide is represented in Schwartz et al unpublished 1996 as follows:



Metoclopramide·HCl
 "highly structured, coplanar form"
 2 hydrogen bonds define structure
 d-2 receptor antagonist

"extended hydrochloride conformation"
 proton away from carbonyl
 2nd hydrogen bond cannot form



Neu-Sensamide™
 "extended side chain conformation"
 1 hydrogen bond defines structure
 poorer binding at d-2 receptor

The formula in the upper left is metoclopramide·HCl in the highly structured, "coplanar" form in which two hydrogen bonds define the structure, this form, dominant at lower (more acid) pH, is a D₂ receptor antagonist. The formula at the upper right represents the "extended hydrochloride conformation" with the proton away from the carbonyl such that the second hydrogen bond (between the carbonyl oxygen and the proton of the side chain ammonium hydrogen) cannot form. The formula at the lower right, representing "Neu-Sensamide™", at higher (less acid, approaching neutral) pH, has an extended side chain conformation, again with only one hydrogen bond (that between the oxygen of the methoxy group and the amide hydrogen), and exhibits poorer binding at the D₂ receptor. In a broader sense, Table 1 also shows that changes in UV absorption at A₂₀₀ detects the conformational difference between acidic and neutral metoclopramide formulations, and as a result, other aryl compounds having N-alkylaminoalkyl substitutions capable of forming a quaternized nitrogen and hydrogen mediating-bonding site, will display a pH sensitive change in their UV spectra at A₂₀₀. For example, 3-amino benzarnide and procaine do not contain either alkylaminodialkyl- or N- substitutions nor do they exhibit pH sensitive UV absorption changes at A₂₀₀ (Table 1). On the other hand, 3-chloro procainamide, procainamide, remoxipride, lidocaine and chlorpromazine all contain N-alkylaminodialkyl substitutions, and they also display UV absorption changes at A₂₀₀.

Table 1. pH sensitive alterations in the UV spectra attributed to proposed conformational changes of the alkylaminodialkyl substructures of agents capable of forming acid addition salts. 100 μ M samples of these agents were acidified to pH 2 and their UV spectra were recorded. These spectra in turn were compared with the UV spectra at ambient pH (i.e. pH 5-6).

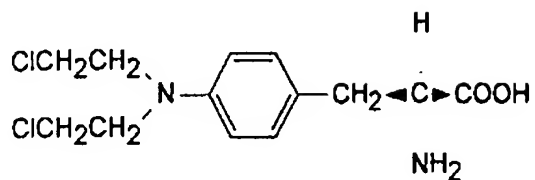
<u>Drug/Agent</u>	<u>A₂₀₀</u>	<u>Comments</u>
(1) 3 Amino benzamide		No N-substitution of benzamide-
Acidic	1.150	no pH change at A ₂₀₀
Aqueous	1.150	
(2) Procaine		O-substituted alkylaminodialkyl
Acidic	1.500	benzoic acid-no pH change at A ₂₀₀
Aqueous	1.500	
(3) Metoclopramide		N-alkylaminodialkyl substituted
Acidic	0.200	benzamide-pH change at A ₂₀₀
Aqueous	1.400	
(4) 3-Chloro procainamide		N-alkylaminodialkyl substituted
Acidic	0.200	benzamide-pH change at A ₂₀₀
Aqueous	2.700	
(5) Procainamide		N-alkylaminodialkyl substituted
Acidic	0.900	benzamide-pH change at A ₂₀₀
Aqueous	2.300	
(6) Remoxipride		N-alkylaminodialkyl substituted
Acidic	0.200	benzamide-pH change at A ₂₀₀
Aqueous	2.800	
(7) Lidocaine		N-alkylaminodialkyl substituted
Acidic	0.180	benzamide-pH change at A ₂₀₀
Aqueous	2.700	
(8) Chlorpromazine		N-alkylaminodialkyl substituted
Acidic	0.200	phenothiazine-pH change at A ₂₀₀
Aqueous	2.600	

Example 4

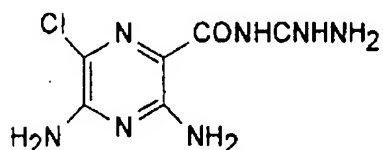
List of drugs capable of forming acid addition salts via the formation of a quaternized nitrogen (e.g. alkylaminodialkyl substitutions), and thereby undergoing pH sensitive alterations, that may consequentially alter drug efficacy or side effects.

The data for this example (obtained from literature, not actual experiment) are presented in Table 2. It lists 143 drugs that are available for clinical use in Sweden (FASS 1992-1996). The data show that the chemical structures and clinical uses of the drugs listed in Table 2 are extremely diverse, but they share a common chemical substitution; namely all have been formulated as acid addition salts (i.e. usually hydrochloride acid salts) because they contain a tertiary nitrogen group (i.e. usually as alkylaminodialkyl substitutions). Because Examples 1-3 establish that compounds containing alkylaminodialkyl substitutions can undergo conformational changes due to pH adjustment, together with the fact that conformation and charge can determine the degree of drug mediated receptor binding antagonism, then Table 2 also show that all the drugs listed are capable of pH modification leading to an altered receptor mediated efficacy or side effect profile.

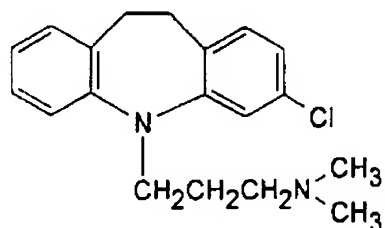
Table 2. List of clinically available acid addition salt drugs including their structures, chemical abstract numbers, trade marks, commercial suppliers and clinical uses. This data has been compiled from the 1992-1996 Sveriges Läkersmedels Information AB, (FASS) and the 1995 Merck Index.

1. MELPHALAN [148-82-3]

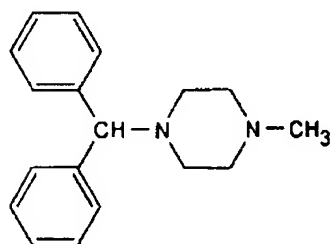
TRADE NAME:	ALKERAN (GLAXO, WELLCOME)
CLINICAL USE:	CYTOSTATIC, ALKYLATING AGENT

2. AMILORIDE [2609-46-3]

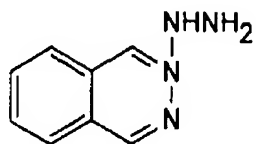
TRADE NAME:	AMILOFERM (NORDIC) AMILORID (NM PHARMA) MIDAMOR (MSD) MODURETIC (MSD) NORMORIX (NYCMED) SPARKAL (SELENA)
CLINICAL USE:	POTASSIUM-SPARING DIURETIC

3. CLOMIPRAMINE [363-49-1]

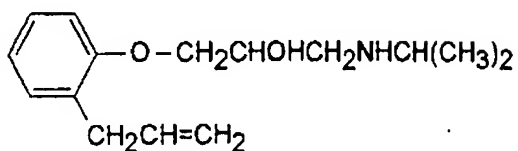
TRADE NAME:	ANAFRANIL (CIBA) KLOMIPRAMIN (NM PHARMA)
CLINICAL USE:	ANTIDEPRESSANT

4. CHLORCYCLIZINE [82-93-9]

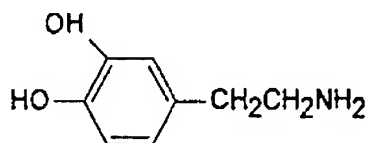
TRADE NAME:	ANERVAN (RECIP) DI-PARALENE (ABBOTT) EXOLYT (ABIGO)
CLINICAL USE:	ANTIHISTAMINE

5. HYDRALAZINE [86-54-4]

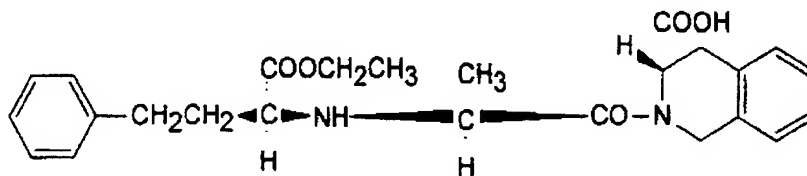
TRADE NAME:	APRESOLIN (CIBA)
CLINICAL USE:	ANTIHYPERTENSIVE

6. ALPRENOLOL [13655-52-2]

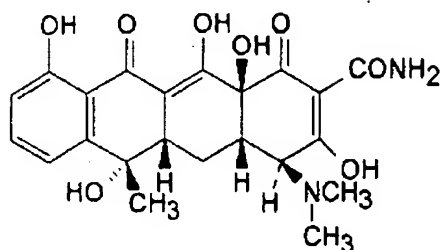
TRADE NAME:	APTIN (HÄSSLE)
CLINICAL USE:	ANTIHYPERTENSIVE ANTIARRHYTHMIC

7. DOPAMINE [51-61-6]

TRADE NAME:	ABBODOP (ABBOTT) GILUDOP (MEDA) INTROPIN (HÄSSLE)
CLINICAL USE:	ADRENERGIC

8. QUINAPRIL [85441-61-8]

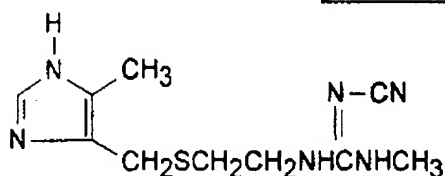
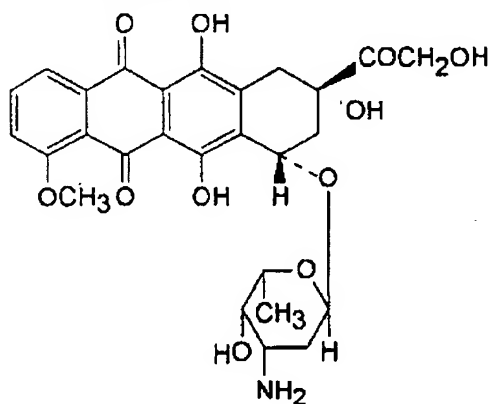
TRADE NAME:	ACCUPRO (PARKE DAVIS)
CLINICAL USE:	ANTIHYPERTENSIVE

9. TETRACYCLINE [60-54-8]

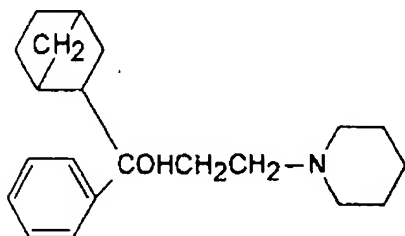
TRADE NAME:	ACHROMYCIN (LEDERLE) ACTISITE (MEDA) TETRACYKLIN (NM PHARMA)
CLINICAL USE:	ANTIBACTERIAL

10. CIMETIDINE [51481-61-9]

TRADE NAME:	ACILOC (ORION) ACINIL (SELENA) CIMETIDIN (SELENA) TAGAMET (SMITH KLINE BEECHA)
CLINICAL USE:	HISTAMINE 2 RECEPTOR ANTIAGONIST, ESPECIALLY IN THE TREATMENT OF DUODENAL AND GASTRIC ULCERS

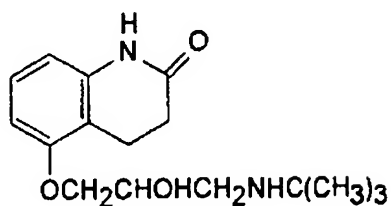
11. DOXORUBICIN [23214-92-8]

TRADE NAME:	ADRIAMYCIN (PHARMACIA & UPJOHN) DOXORUBICIN (NYCOMED)
CLINICAL USE:	ANTINEOPLASTIC

12. BIPERIDEN [514-65-8]

TRADE NAME:	AKINETON (MEDA)
CLINICAL USE:	ANTICHOLINERGIC ANTIPARKINSON

TRADE NAME:	ARTEOPTIC (CIBA VISION)
CLINICAL USE:	β -RECEPTOR BLOCKER

CN(C)CC(=O)OCCN(C)C=O

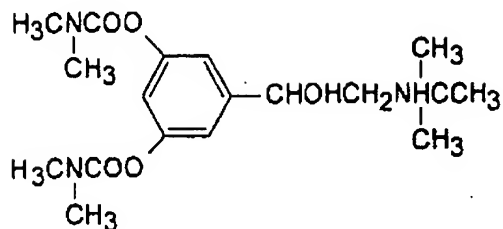
TRADE NAME:	ARTONIL (SELENA) ZANTAC (GLAXO WELLCOME)
CLINICAL USE:	ANTIULCERATIVE

OCCOCCN1CCN(CC2=CC=CC=C2C3=CC=CC=C3Cl)CC1

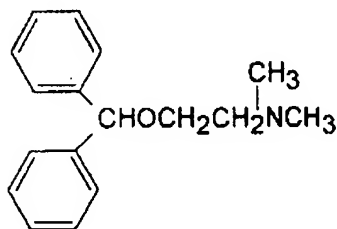
TRADE NAME:	ATARAX (UCB) HISTILOS (UCB) VISTARIL (ROERIG)
CLINICAL USE:	TRANQUILIZER

CN(C)[C@H]1[C@@H](O)[C@H](C(=O)O)[C@@H](O)[C@H]1C(=O)O[C@H]2[C@@H](O)[C@H](C(=O)O)[C@@H](O)[C@H]2C(=O)O[C@H]3C(=O)O[C@H](Cl)[C@@H](O)[C@H]3O

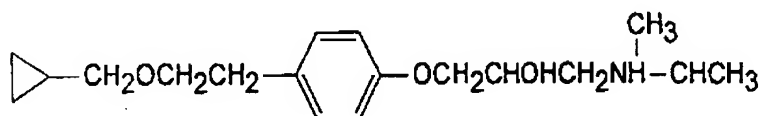
TRADE NAME:	AUREOMYCIN (LEDERLE)
CLINICAL USE:	ANTIBIOTIC

17. BAMBUTEROL

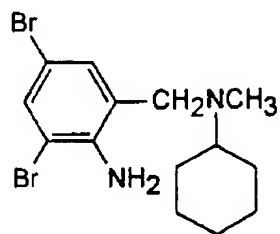
TRADE NAME:	BAMBEC (DRACO)
CLINICAL USE:	BRONCHODIALATOR

18. DIPHENHYDRAMINE [482-05-3]

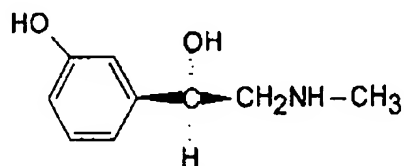
TRADE NAME:	BENYLAN (PARK-DAVIS) DESENTOL (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTI-HISTAMINE ANTI-MOTIONSICKNESS

19. BETAXOLOL [63659-18-7]

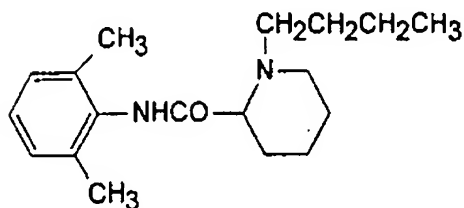
TRADE NAME:	BETOPTIC (ALCON) KERLON (SEARLE)
CLINICAL USE:	ANTI-GLAUCOMA ANTI-HYPERTENSIVE

20. BROMHEXINE [3572-43-8]

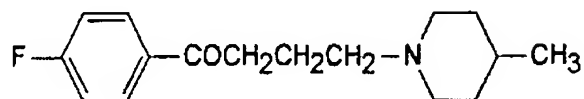
TRADE NAME:	BISOLVON (BOEHRINGER) BROMHEXIN (ACO) MOLLIPECT (TIKA)
CLINICAL USE:	MUCOLYTIC EXPECTORANT

21. PHENYLEPHRINE HYDROCHLORIDE [61-76-7]

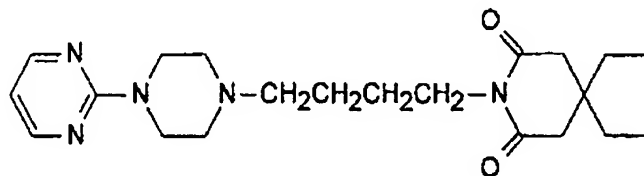
TRADE NAME:	BLEFCON (ALLERGAN) METAOXEDRIN (MEDA) NEOSYNEPHRINE (SANOFI WINTHROP) ZINCFRIN (ALCON)
CLINICAL USE:	ADRENERGIC

22. BUPIVACAINE [2180-92-9]

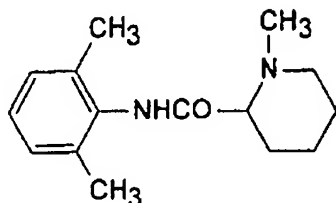
TRADE NAME:	BUPIVAKAIN (NORCOX) MARCAIN (ASTRA)
CLINICAL USE:	LOCAL ANAESTHETIC

23. MELPERONE [3575-80-2]

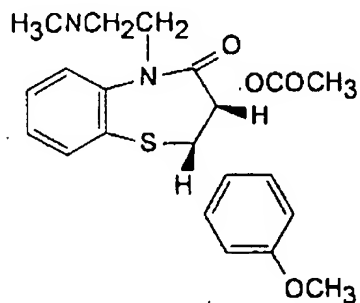
TRADE NAME:	BURONIL (LUNDBECK)
CLINICAL USE:	NEUROLEPTIC

24. BUSPIRONE [36505-84-7]

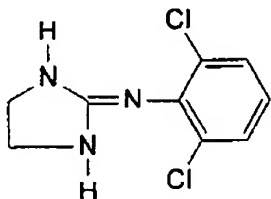
TRADE NAME:	BUSPAR (BRISTOL-MEYERS SQUIBB)
CLINICAL USE:	ANXIOLYTIC

25. MEPIVACAINE [96-88-8]

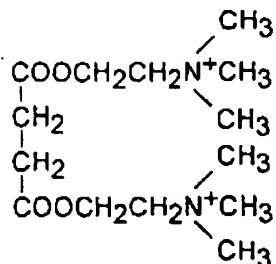
TRADE NAME:	CARBOCAIN (ASTRA)
CLINICAL USE:	LOCAL ANAESTHETIC

26. DILTIAZEM [42399-41-7]

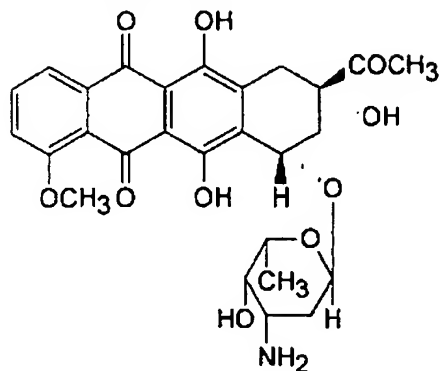
TRADE NAME:	CARDIZEM (PHARMACIA & UPJOHN) ENTRYDIL (ORION) TILDIEM (TIKA)
CLINICAL USE:	CALCIUM ANTAGONIST VASODILATOR

27. CLONIDINE [4205-90-7]

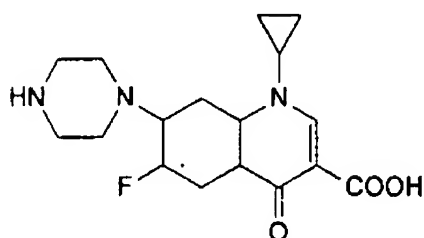
TRADE NAME:	CATAPRESAN (BOEHRINGER INGELHEIM)
CLINICAL USE:	ANTIHYPERTENSIVE

28. SUCCINYLCHOLINE CHLORIDE [71-27-2]

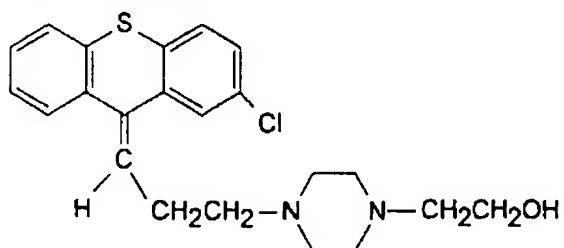
TRADE NAME:	CELOCURIN (PHARMACIA & UPJOHN)
CLINICAL USE:	SKELETAL MUSCLE RELAXANT (SHORT DURATION)

29. DAUNORUBICIN [20830-81-3]

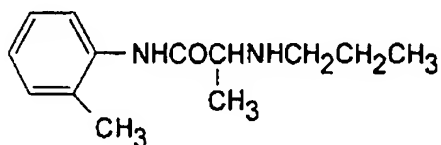
TRADE NAME:	CERUBIDIN (RHONE-POULENC RORER) DAUNOXOME (SWEDISH ORPHAN)
CLINICAL USE:	CYTOSTATIC

30. CIPROFLOXACINE [85721-33-1, 86393-32-0(HCl)]

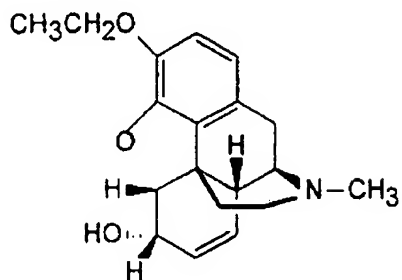
TRADE NAME:	CILOXAN (ALCON) CIPROXIN (BAYER)
CLINICAL USE:	ANTIBACTERIAL

31. CLOPENTHIXOL [982-24-1]

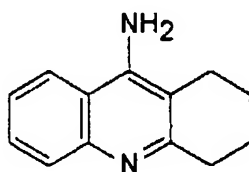
TRADE NAME:	CISORDINOL (LUNDBECK)
CLINICAL USE:	ANTIPSYCHOTIC

32. PRILOCAINE [721-50-6]

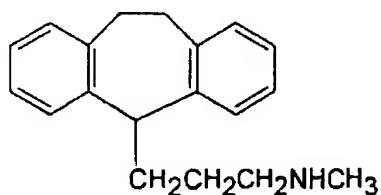
TRADE NAME:	CITANEST (ASTRA) EMLA (ASTRA)
CLINICAL USE:	LOCAL ANAESTHETIC

33. ETHYLMORPHINE [76-58-4]

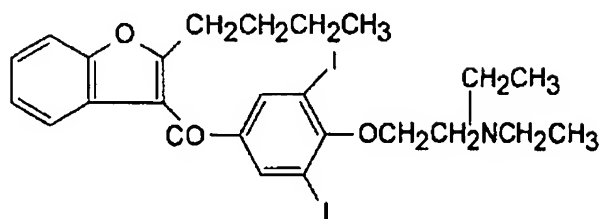
TRADE NAME:	COCILLANA - ETYFIN (PHARMACIA & UPJOHN) COSYLA (PARKE-DAVIS) LEPHETON (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTITUSSIVE

34. TACRINE [321-64-2]

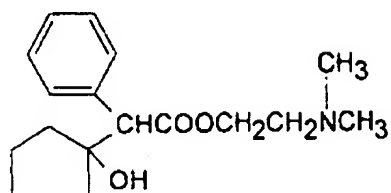
TRADE NAME:	COGNEX (PARKE-DAVIS)
CLINICAL USE:	CHOLINERGIC

35. PROTRIPTYLINE [438-60-8]

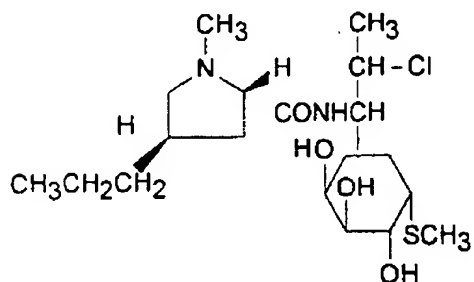
TRADE NAME:	CONCORDIN (MSD)
CLINICAL USE:	ANTIDEPRESSANT

36. AMIODARONE [1951-25-3]

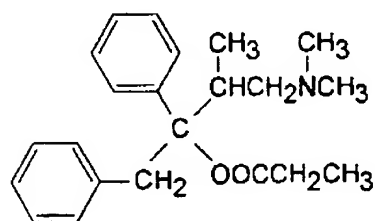
TRADE NAME:	CORDARONE (SANOFI WINTHROP)
CLINICAL USE:	ANTIARRYHYTHMIC

37. CYCLOPENTOLATE [512-15-2]

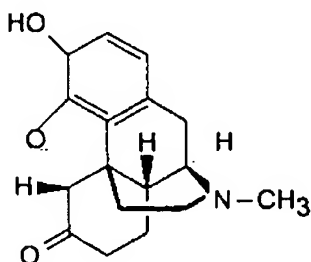
TRADE NAME:	CYCLOGYL (ALCON) CYCLOPENTOLAT (MEDA)
CLINICAL USE:	ANTICHOLINERGIC

38. CLINDAMYCIN [18323-44-9]

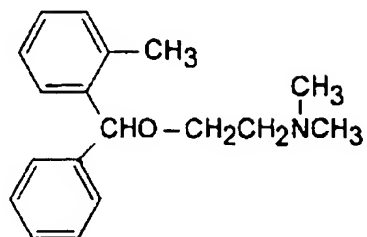
TRADE NAME:	DALACIN (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTIBIOTIC

39. PROPOXYPHENE [469-62-5]

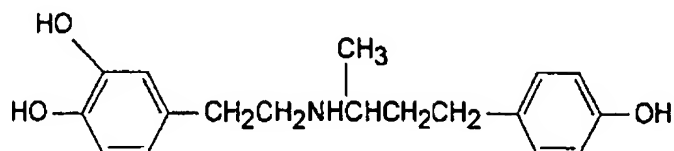
TRADE NAME:	DEXODON (TIKA) DEXOFEN (ASTRA) DISTALQESIC (LILLY) DOLERON (ASTRA) DOLOTARD (NYCOMED) DOLOXENE (LILLY) PARAFLEX (ASTRA)
CLINICAL USE:	ANALGESIC

40. HYDROMORPHONE [466-99-9]

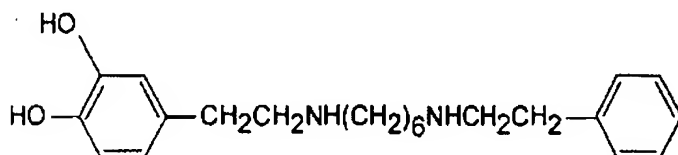
TRADE NAME:	DILAUDID (MEDA)
CLINICAL USE:	ANALGESIC

41. ORPHENADRINE [83-98-7]

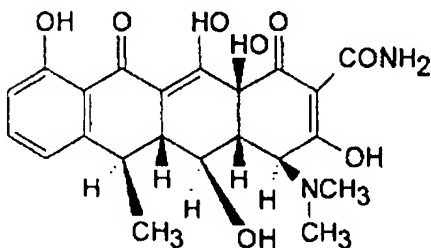
TRADE NAME:	DISIPAL (YAMANOUCHI) NORFLEX (3M) NORGESIC (3M)
CLINICAL USE:	MUSCLE RELAXANT (SCELETETAL) ANTIPARKINSON

42. DOBUTAMINE [30468-04-2]

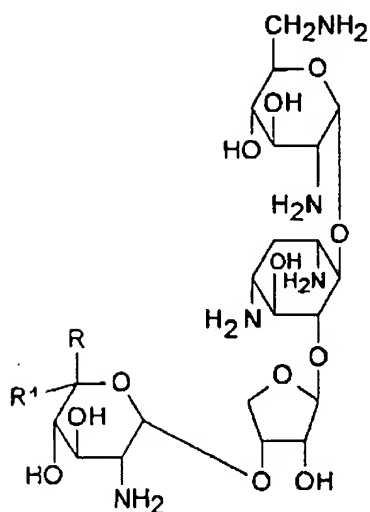
TRADE NAME:	DOBUJECT (LEIRAS) DOBUTREX (LILLY)
CLINICAL USE:	CARDIOTONIC

43. DOPEXAMINE [86494-91-5(HYDROCHLORIDE)]

TRADE NAME:	DOPACARD (FISONS)
CLINICAL USE:	CARDIOTONIC

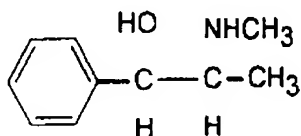
44. DOXYCYCLINE [564-25-0]

TRADE NAME:	DORYX (SCAND PHARM) DOXYCYKLIN (ENAPHARM) DOXYFERM (NORDIC) IDOCYKLIN (ROERIG) VIBRAMYCIN (PFIZER)
CLINICAL USE:	ANTIBACTERIAL

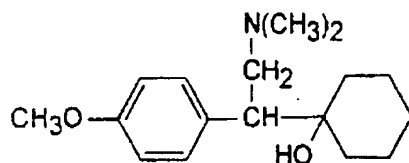
45. NEOMYCIN [1404-04-2, FOR THE MIXTURE]

TRADE NAME:	ECOMYTRIN (LUNDBECK) CELESTON (SCHERING-PLOUGH) DECARDRON (MSD) ISOPTO - BIOTIC (ALCON) NEBACETIN (LUNDBECK)
CLINICAL USE:	ANTIBACTERIAL

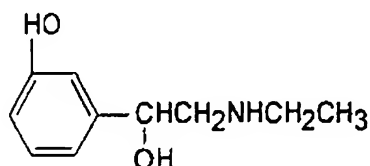
NEOMYCIN B R = H, R¹ = CH₂NH₂
NEOMYCIN C R = CH₂NH₂, R¹ = H

46. EPHEDRINE [50-98-6]

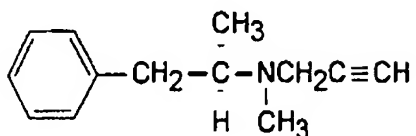
TRADE NAME:	EFEDRIN (NM PHARMA) LEPHETON (PHARMACIA & UPJOHN) LERGIQAN (RECIP) MOLLIPECT (TIKA)
CLINICAL USE:	ADRENERGIC

47. VENLAFAXINE {}

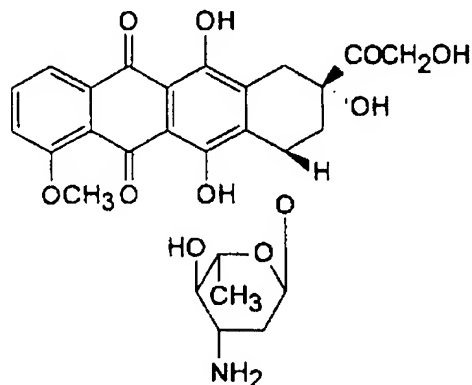
TRADE NAME:	EFEXOR (WYETH)
CLINICAL USE:	ANTIDEPRESSANT

48. ETILEFRIN [709-55-7]

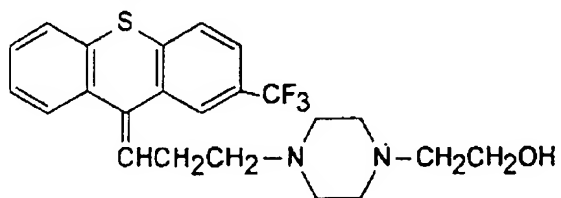
TRADE NAME:	EFFORTIL (BOEHRINGER INGELHEIM)
CLINICAL USE:	ADRENERGIC DOPAMINERGIC ANTIHYPERTENSIVE

49. DEPRENYL [2323-36-6]

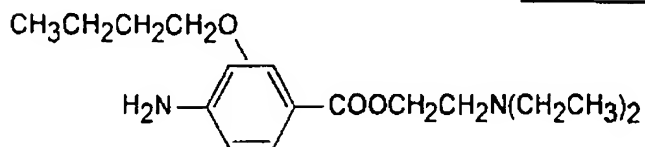
TRADE NAME:	ELDEPRYL (ORION) SELEGILIN (NM PHARMA)
CLINICAL USE:	ANTIPARKINSON

50. EPIRUBICIN [56390-09-1(HCl), 56420-45-2(BAS)]

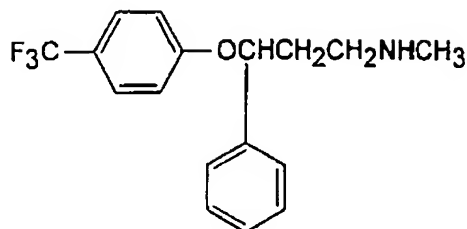
TRADE NAME:	FARMORUBICIN (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTINEOPLASTIC ANTIBIOTIC

51. FLUPENTIXOL [2709-56-0]

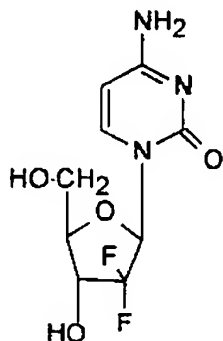
TRADE NAME:	FLUANXOL (LUNDBECK)
CLINICAL USE:	ANTIPSYCHOTIC

52. BENOXINATE [99-43-4]

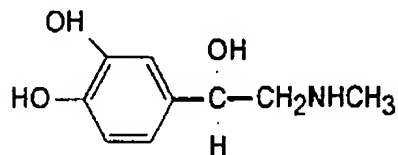
TRADE NAME:	FLURESS (ABIGO) OXIBUPROKAIN (MEDA)
CLINICAL USE:	ANAESTHETIC (TOPICAL)

53. FLUOXETIN [54910-89-3]

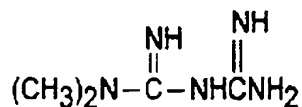
TRADE NAME:	FONTEX (LILLY)
CLINICAL USE:	ANTIDEPRESSANT

54. GEMCITABINE []

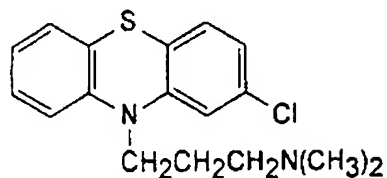
TRADE NAME:	GEMZAR (LILLY)
CLINICAL USE:	ANTINEOPLASTIC

55. ADRENALINE/EPINEPHRINE []

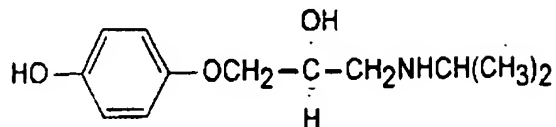
TRADE NAME:	CITANEST ADRENALIN (ASTRA) EPPY (ABIGO) GLAUFRIN (ALLERGAN) MARCAIN ADRENALIN (ASTRA) XYLOCAIN ADRENALIN (ASTRA)
CLINICAL USE:	ADRENERGIC

56. METFORMIN [657-24-9]

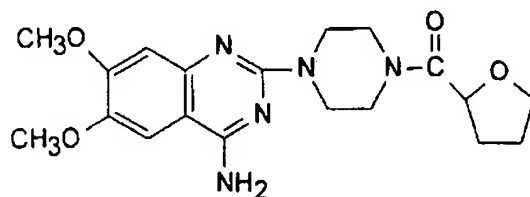
TRADE NAME:	GLUCOPHAGE (MEDA)
CLINICAL USE:	ANTIDIABETIC

57. CHLORPROMAZINE [50-53-3]

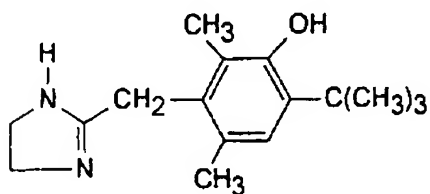
TRADE NAME:	HIBERNAL (RHONE-POULENCE RORER)
CLINICAL USE:	ANTI-EMETIC TRANQUILIZER SEDATIVE

58. PRENALTEROL [57526-81-5]

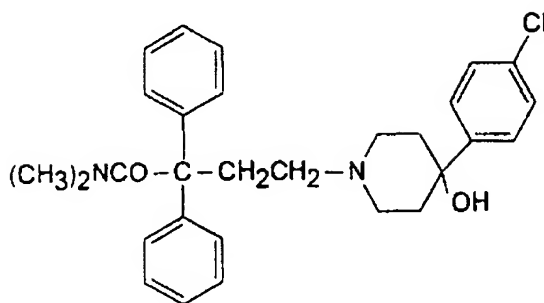
TRADE NAME:	HYPRENAN (HÄSSLE)
CLINICAL USE:	ADRENERGIC

59. TERAZOSINE [63590-64-7, 70024-40-7 (HYDROCHLORIDE)]

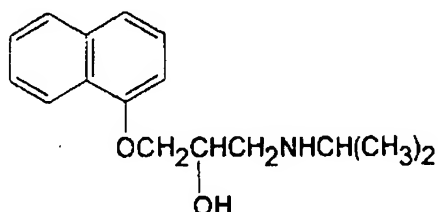
TRADE NAME:	HYTRINEX (ASTRA) SINALFA (SINALFA ABBOTT)
CLINICAL USE:	ANTIHYPERTENSIVE

60. OXYMETAZOLINE [1491-59-4]

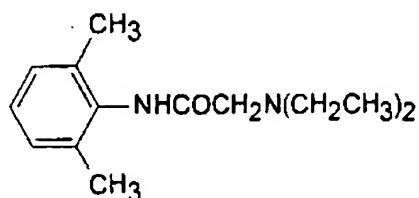
TRADE NAME:	LLIADIN (MEDA) NASIN (TIKA) NEZERIL (DRACO) ZOLIN (ACO)
CLINICAL USE:	ADRENERGIC

61. LOPERAMIDE [53179-11-6]

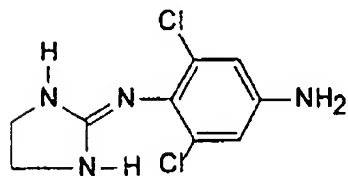
TRADE NAME:	IMODIUM (JENSSEN-CILAG) LOPERAMID (SCAND PHARM) PRIMODIUM (JENSSEN-CILAG) TRAVELLO (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTIDIARETIC

62. PROPRANOLOL [525-66-6]

TRADE NAME:	INDERAL (ZENECA) PROPRANOLOL (NM PHARMA)
CLINICAL USE:	β-ADRENERGIC BLOCKER ANTIARRHYTHMIC

63. LIDOCAINE [137-58-6]

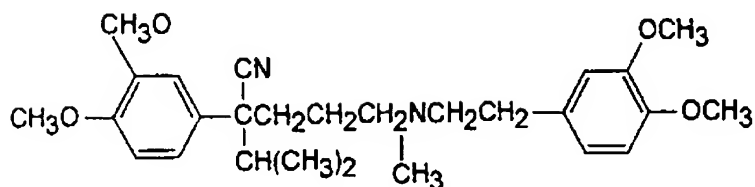
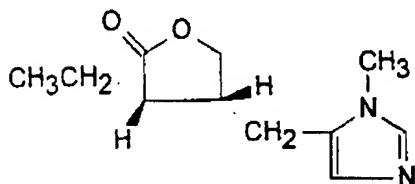
TRADE NAME:	DEPO - MEDROL (PHARMACIA & UPJOHN) EMLA (ASTRA) INSTILLAGEL (ELLEM) LEDERSPAN (LEDERLE) XYLOCAIN (ASTRA) XYLOCARD (ASTRA) XYLOPROCT (ASTRA)
CLINICAL USE:	LOCAL ANAESTHETIC

64. APRACLONIDINE [66711-21-5]

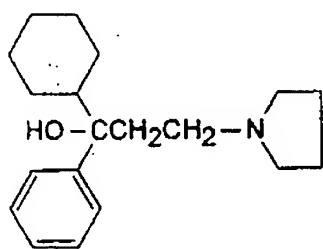
TRADE NAME:	LOPIDINE (ALCON)
CLINICAL USE:	TREATMENT OF POSTSURGICAL ELEVATED INTRAOCULAR PRESSURE

65. VERAPAMIL [52-53-9]

TRADE NAME:	ISOPTIN (MEDA) VERALOC (ORION) VERAPAMIL (NM PHARMA)
CLINICAL USE:	ANTIARRHYTHMIC VASODILATOR

66. PILOCARPINE [92-13-7]

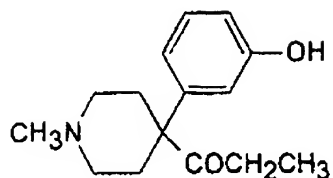
TRADE NAME:	FOTIL (LEIRAS) ISOPTO - PILOKARPIN (ALCON) LICARPIN (ALLERGAN) PILOKARPIN (MEDA) SPERSACARPINE (CIBA) TIMPILO (MSD)
CLINICAL USE:	ANTIGLAUCOMA CHOLINERGIC

67. PROCYCLIDINE [77-37-2]

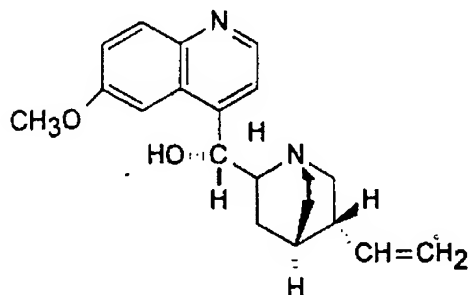
TRADE NAME:	KEMADRIN (GLAXO WELLCOME)
CLINICAL USE:	ANTIPARKINSON

68. KETAMINE [6740-88-1]

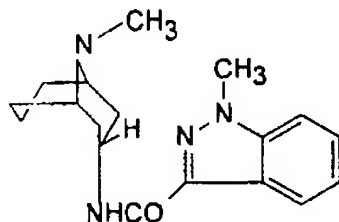
TRADE NAME:	KETALAR (PARKE-DAVIS)
CLINICAL USE:	GENERAL ANAESTHETIC

69. KETOBEMIDON []

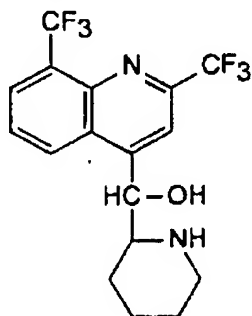
TRADE NAME:	KETOGAN (NOVUM-LUNDBECK)
CLINICAL USE:	ANALGETIC SPASMOLYTIC

70. QUINIDINE [130-95-0, 60-93-5(HYDROCHLORIDE)]

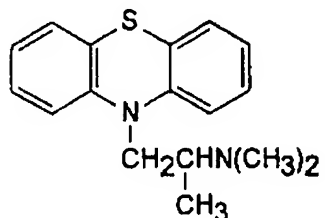
TRADE NAME:	KININ (NM PHARMA)
CLINICAL USE:	ANTIMALARIAL

71. GRANISETRONE [109889-09-0, 107007-99-8(HYDROCHLORIDE)]

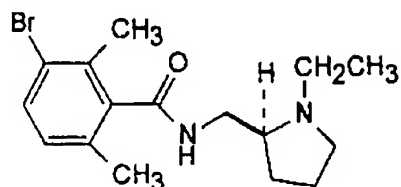
TRADE NAME:	KYTRIL (SMITH KLINE BEECHAM)
CLINICAL USE:	ANTIEMETIC

72. MEFLOQUIN [51773-92-3(HYDROCHLORIDE)]

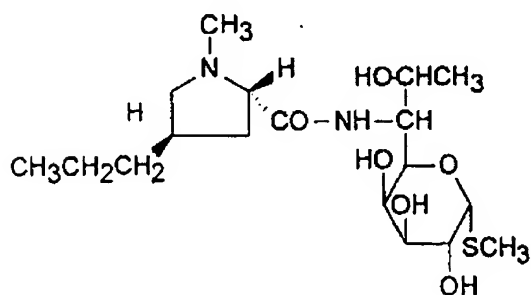
TRADE NAME:	LARIAM (ROCHE)
CLINICAL USE:	ANTIMALARIAL

73. PROMETHAZINE [7440-12-12]

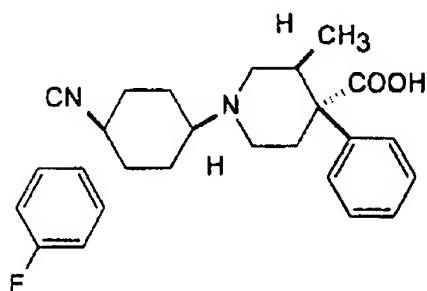
TRADE NAME:	LERGIGAN (RECIP)
CLINICAL USE:	ANTI-HISTAMINE

74. REMOXIPRIDE []

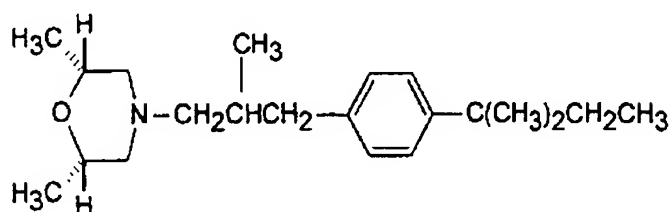
TRADE NAME:	ROXIAM (ASTRA)
CLINICAL USE:	NEUROLEPTIC

75. LINCOMYCIN [154-21-2]

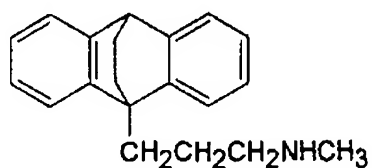
TRADE NAME:	LINCOCIN (UPJOHN)
CLINICAL USE:	ANTIBIOTIC

76. LEVOCABASTIN []

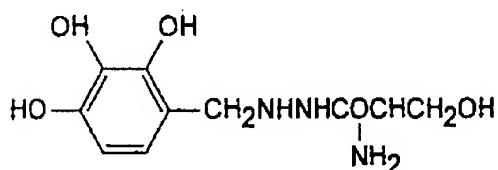
TRADE NAME:	LIVOSTIN (JENSSEN-CILAG)
CLINICAL USE:	H ₁ -ANTAGONIST

77. AMOROLFINE [78613-35-1, 78613-38-4(HYDROCHLORIDE)]

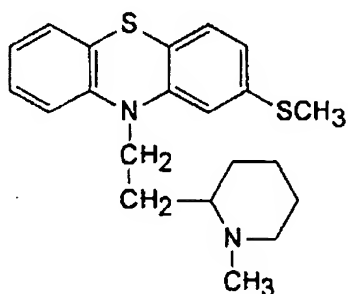
TRADE NAME:	LOCERYL (ROCHE)
CLINICAL USE:	ANTIMYCOTIC

78. MAPROTILINE [10260-69-8]

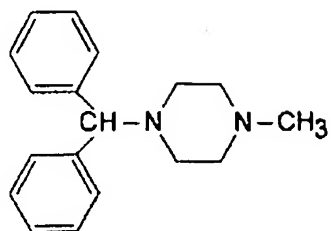
TRADE NAME:	LUDIOMIL (CIBA) MAPROTILIN (NM PHARMA)
CLINICAL USE:	ANTIDEPRESSANT

79. BENSERAZIDE [322-35-0]

TRADE NAME:	MADOPARK (ROCHE)
CLINICAL USE:	ANTIPARKINSON DOPAMINERGIC

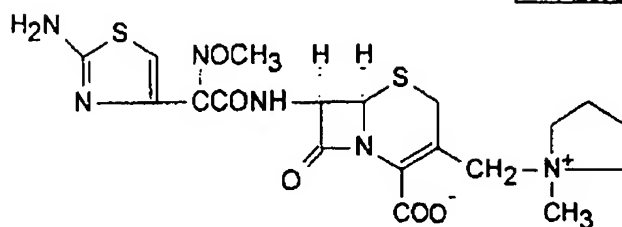
80. THIORIDAZINE [50-52-2]

TRADE NAME:	MALLOROL (SANDOZ)
CLINICAL USE:	NEUROLEPTIC

81. CYCLIZINE [82-92-8]

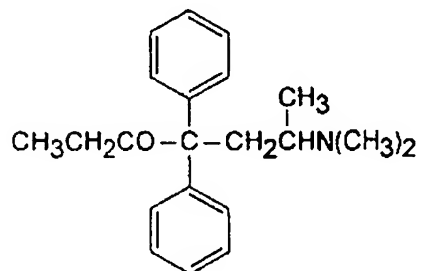
TRADE NAME: MARZINE
(GLAXO WELLCOME)

CLINICAL USE: ANITHISTAMINE
ANTIEMETIC

82. CEPHEPIME []

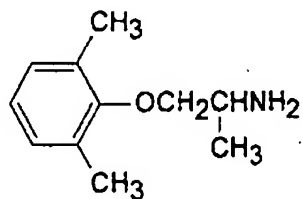
TRADE NAME: MAXIPIME
(BRISTOL-MEYERS SQUIBB)

CLINICAL USE: ANTIBIOTIC

83. METHADONE [1095-90-5]

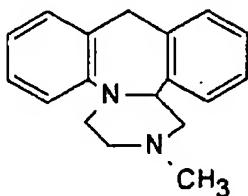
TRADE NAME: METADON
(PHARMACIA & UPJOHN)

CLINICAL USE: NARCOTIC ANALGETIC

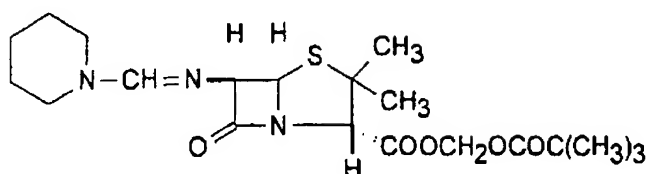
84. MEXILETINE [31828-71-4]

TRADE NAME: MEXITIL
(BOEHRINGER INGELHEIM)

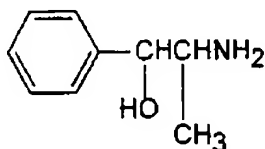
CLINICAL USE: ANTIARRHYTHMIC

85. MIANSERIN [24219-97-4]

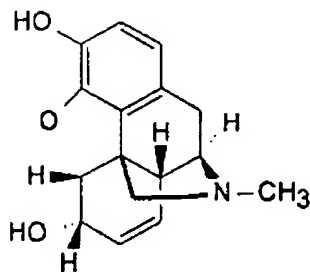
TRADE NAME:	MIANSERIN (NM PHARMA) TOLVON (ORGANON)
CLINICAL USE:	ANTIDEPRESSANT

86. PIVMECILLINAM []

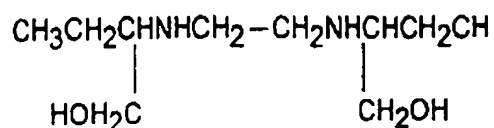
TRADE NAME:	MIRAXID (LÖVENS)
CLINICAL USE:	ANTIBACTERIAL

87. PHENYLPROPANOLAMINE [154-41-61]

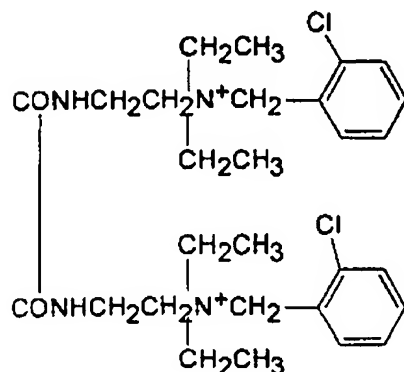
TRADE NAME:	LUNERIN (TIKA) MONYDRIN (TIKA) RINEXIN (RECIP) RINOMAR (RECIP)
CLINICAL USE:	VASOCONSTRICTOR ADRENERGIC

88. MORPHINE [52-27-2]

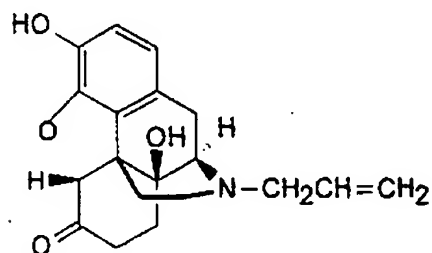
TRADE NAME:	DOLCONTIN (PHARMACIA & UPJOHN) LOCEPTIN (NYCOMED) MAXIDON (ASTRA) MORFIN (PHARMACIA & UPJOHN) SPASMOFEN (ABIGO)
CLINICAL USE:	NARCOTIC ANALGESIC

89. ETHAMBUTOL [304-84-7]

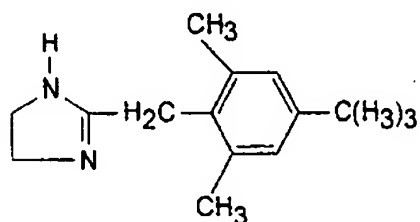
TRADE NAME:	MYAMBUTOL (LEDERLE)
CLINICAL USE:	TUBERCULOSTATIC

90. AMBENONIUM CHLORIDE [115-79-7]

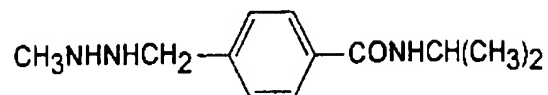
TRADE NAME:	MYTELASE (SANOFI WINTHROP)
CLINICAL USE:	CHOLINESTERASE INHIBITOR

91. NALOXONE [465-65-6]

TRADE NAME:	NARCANTI (MEDA)
CLINICAL USE:	ANTAGONIST (TO NARCOTICS)

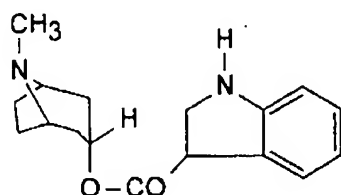
92. XYLOMETAZOLINE [526-36-3]

TRADE NAME:	NASOFORM (NORDIC) OTRIVIN (CIBA)
CLINICAL USE:	ADRENERGIC VASOCONSTRICTOR

93. PROCARBAZINE [671-16-9]

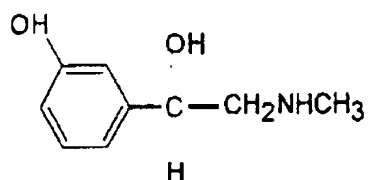
TRADE NAME: NATULANAR (ROCHE)

CLINICAL USE: ANTINEOPALSTIC

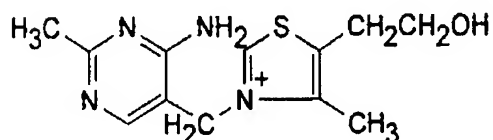
94. TROPISETRONE []

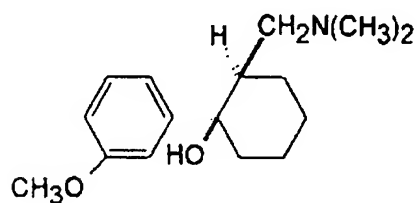
TRADE NAME: NAVOBAN (SANDOZ)

CLINICAL USE: ANTIEMETIC

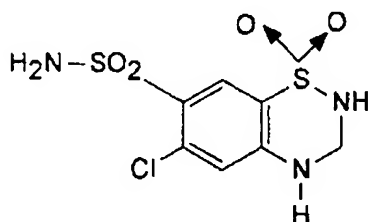
95. PHENYLEPHRINE [61-76-7(HYDROCHLORIDE)]
 TRADE NAME: BLEFCON (ALLERGAN)
 ISOPTO-BIOTIC (ALCON)
 METAOXEDRIN (MEDA)
 NEOSYNEPHRINE
 (SANOFI WINTHROP)
 ZINCFRIN (ALCON)

CLINICAL USE: ADRENERGIC

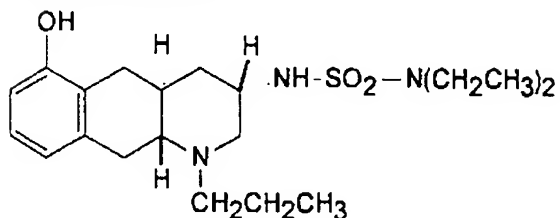
96. THIAMINE [67-03-8]TRADE NAME: ASTRATONIL FORTE (ASTRA)
BETABION (MEDA)CLINICAL USE: ENZYME
CO-FACTOR-VITAMIN B1

97. TRAMADOL [27203-92-5, 22204-88-2(HYDROCHLORIDE)]

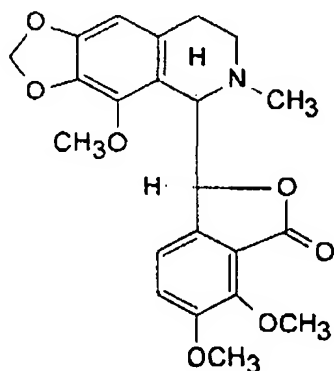
TRADE NAME:	NOBLIGAN (SEARLE)
CLINICAL USE:	ANALGESIC

98. HYDROCHLOROTIAZID [58-93-5]

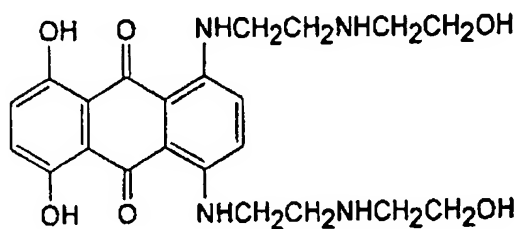
TRADE NAME:	SPARKAL (SELENA) TRIATEC COMP (HOECHST) AMILOFERM (NORDIC)
CLINICAL USE:	DIURETIC

99. QUINAGOLIDE []

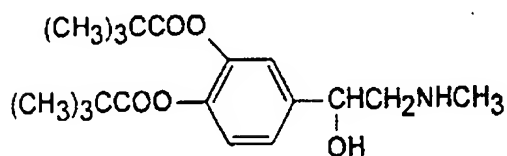
TRADE NAME:	NORPROLAC (SANDOZ)
CLINICAL USE:	PROLACTIN ANTAGONIST

100. NOSCAPINE [128-62-1, 912-60-7(HYDROCHLORIDE)]

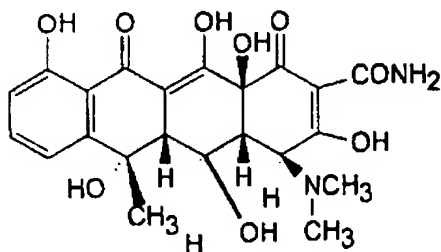
TRADE NAME:	NIPAXON (PHARMACIA & UPJOHN) NOSKAPIN (ACO) SPAMOFEN (ABIGO)
CLINICAL USE:	ANTITUSSIVE

101. MITOXANTRONE [65271-80-90, 76476-82-3(HYDROCHLORIDE)]

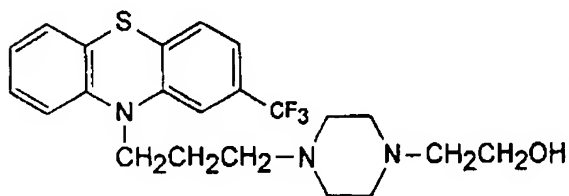
TRADE NAME:	NOVANTRONE (LEDERLE)
CLINICAL USE:	ANTINEOPALSTIC

102. DIPIVEFRIN [52365-63-6, 64019-93-8(HYDROCHLORIDE)]

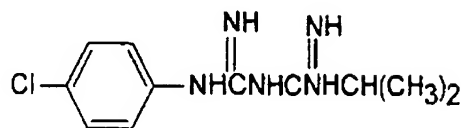
TRADE NAME:	OFTAPINEX (LEIRAS) PROPINE (ALLERGAN)
CLINICAL USE:	ANTI-GLAUCOMA ADRENERGIC

103. OXYTETRACYCLINE [79-57-2, 2058-46-0(HYDROCHLORIDE)]

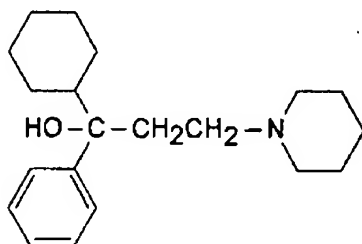
TRADE NAME:	OXYTETRAL (DUMEX) TERRACORTIL (PFIZER) TERRAMYCIN (PFIZER)
CLINICAL USE:	ANTIBIOTIC

104. FLUPHENAZINE [69-23-8, 146-56-5(HYDROCHLORIDE)]

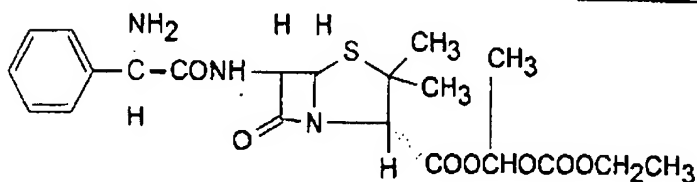
TRADE NAME:	PACINOL (SCHERING- PLOUGH) SIQUALONE (BRISTOL MEYERS-SQUIBB)
CLINICAL USE:	ANTIPSYCHOTIC

105. CHLORGUANIDE [500-92-5]

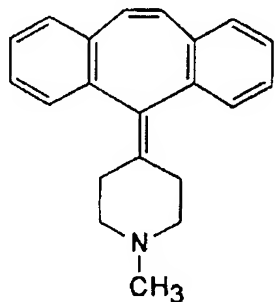
TRADE NAME:	PALUDRINE (ZENECA)
CLINICAL USE:	ANTIMALARIAL

106. TRIHENYPHENIDYL [52-49-3]

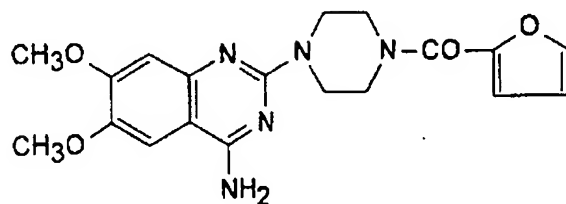
TRADE NAME:	PARGITAN (ABIGO)
CLINICAL USE:	ANTIPARKINSON

107. BACAMPICILLIN [50972-17-3, 37661-08-8(HYDROCHLORIDE)]

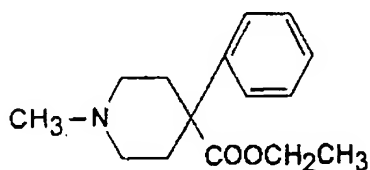
TRADE NAME:	PENGLOBE (ASTRA)
CLINICAL USE:	ANTIBACTERIAL

108. CYPROHEPTADINE [129-03-3, 41354-29-4(HYDROCHLORIDE)]

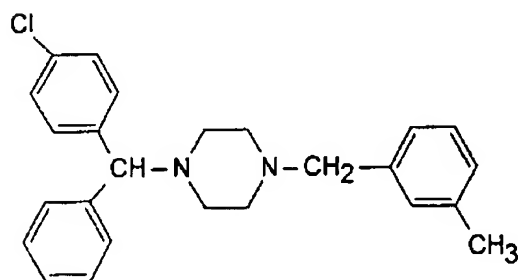
TRADE NAME:	PERIACTIN (MSD)
CLINICAL USE:	H1 ANTAGONIST ANTIHISTAMINE

109. PRAZOSIN [19216-56-9, 19237-84-4(HYDROCHLORIDE)]

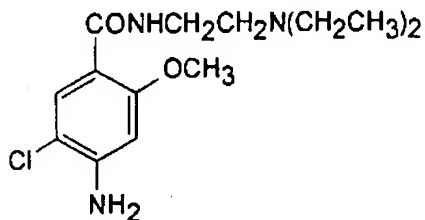
TRADE NAME:	PERIPRESS (PFIZER)
CLINICAL USE:	α 1-ADRENERGIC BLOCKER ANTIHYPERTENSIVE

110. MEPERIDINE [57-42-1, 50-13-5(HYDROCHLORIDE)]

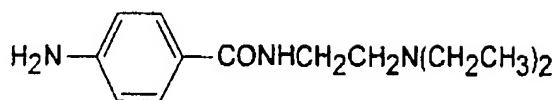
TRADE NAME:	PETIDIN (PHARMACIA & UPJOHN)
CLINICAL USE:	NARCOTIC ANALGETIC

111. MECLIZINE [569-65-3, 31884-77-2(HYDROCHLORIDE)]

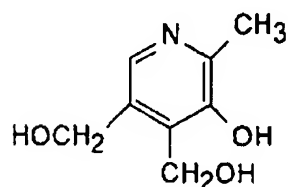
TRADE NAME:	HISTILOS (UCB) POSTAFEN (UCB)
CLINICAL USE:	ANTIEMETIC

112. METOCLOPRAMIDE [364-62-5, 54143-57-6(HYDROCHLORIDE)]

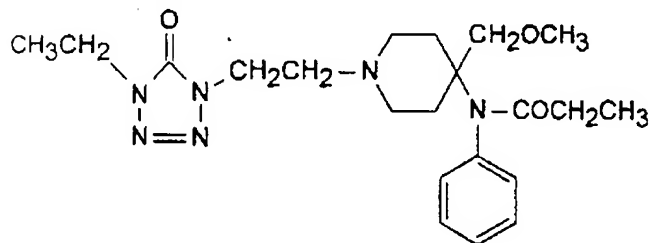
TRADE NAME:	PRIMPERAN (LUNDBECK)
CLINICAL USE:	ANTIEMETIC

113. PROCAINAMIDE [614-39-1]

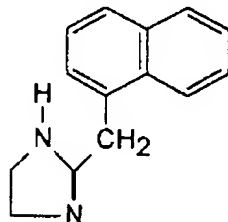
TRADE NAME:	PROKAINAMID (HÄSSLE)
CLINICAL USE:	ANTIARRHYTHMIC

114. PYRIDOXINE [58-56-0]

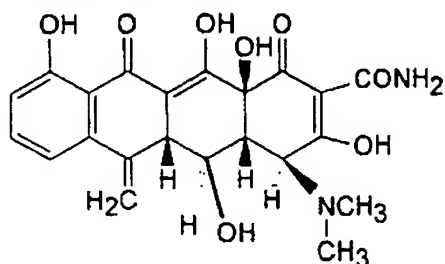
TRADE NAME:	ASTRANOIL FORTE (ASTRA)
CLINICAL USE:	VITAMIN B6

115. ALFENTANIL [71195-28-6, 70879-28-6(HYDROCHLORIDE)]

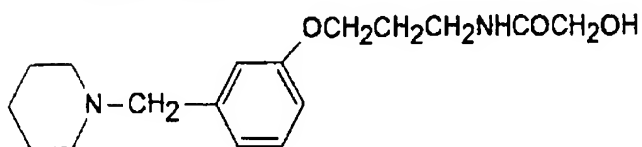
TRADE NAME:	RAPIFEN (JENSSEN-CILAG)
CLINICAL USE:	NARCOTIC ANALGESIC

116. NAPHAZOLINE [835-31-4, 550-29-2(HYDROCHLORIDE)]

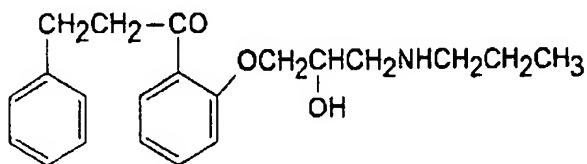
TRADE NAME:	ANTASTEN-PRIVIN (CIBA VISION) RIMIDOL (UCB)
CLINICAL USE:	ADRENERGIC (VASOCONSTRICTOR DECONGESTANT)

117. METHACYCLINE [914-00-1, 3963-95-9(HYDROCHLORIDE)]

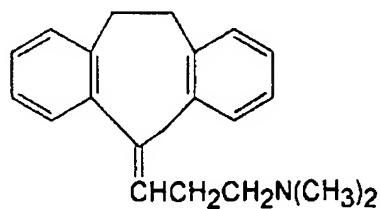
TRADE NAME:	RONDONYCIN (ROERIG)
CLINICAL USE:	ANTIBACTERIAL

118. ROXATIDINE []

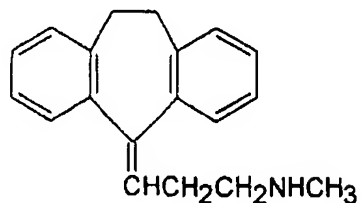
TRADE NAME:	ROXIT (HOECHST)
CLINICAL USE:	ANTI-ULCERATIVE

119. PROPAFENONE [54063-53-5, 34183-22-7(HYDROCHLORIDE)]

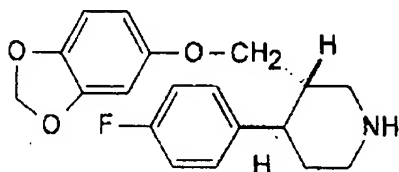
TRADE NAME:	RYTMONORM (MEDA)
CLINICAL USE:	ANTIARRHYTHMIC

120. AMITRIPTYLINE [50-48-6, 549-18-8(HYDROCHLORIDE)]

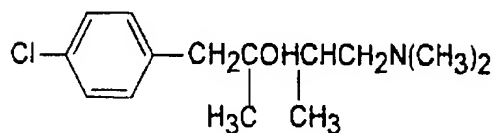
TRADE NAME:	SAROTEN (LUNDBECK) TRYPTIZOL (MSD)
CLINICAL USE:	ANTIDEPRESSANT

121. NORTRIPTYLINE [72-69-5, 894-71-3(HYDROCHLORIDE)]

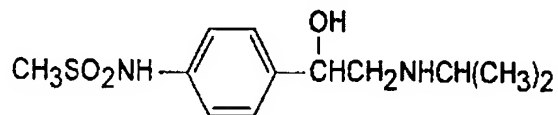
TRADE NAME:	SENSAVAL (LUNDBECK)
CLINICAL USE:	ANTIDEPRESSANT

122. PAROXETINE [61869-08-7]

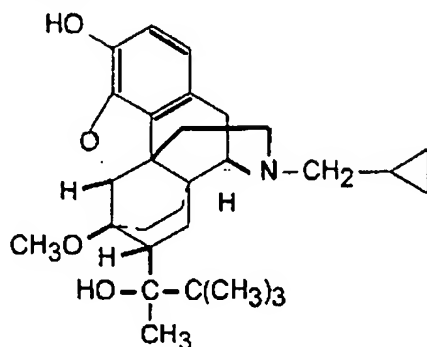
TRADE NAME:	SEROXAT (NOVO NORDISK)
CLINICAL USE:	ANTIDEPRESSANT

123. CLOBUTINOL [14860-49-2]

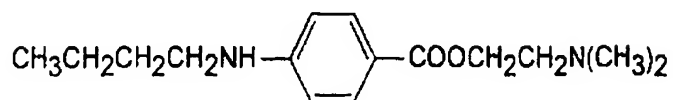
TRADE NAME:	SILOMAT (BOEHRINGER INGELHEIM)
CLINICAL USE:	ANTITUSSIVE

124. SOTALOL [3930-20-9, 959-24-0(HYDROCHLORIDE)]

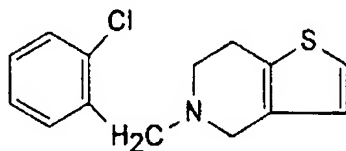
TRADE NAME:	SOTACOR (BRISTOL-MEYERS SQUIBB) SOTALOL (NM PHARMA)
CLINICAL USE:	ANTIANGINAL ANTIARRHYTHMIC ANTIHYPERTENSIVE

125. BUPRENORPHINE [52485-79-7, 53152-21-9(HYDROCHLORIDE)]

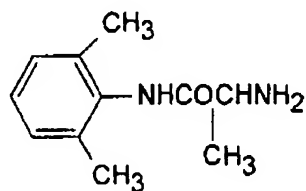
TRADE NAME:	TEMGESIC (MEDA)
CLINICAL USE:	ANALGESIC

126. TETRACAINE [136-47-0]

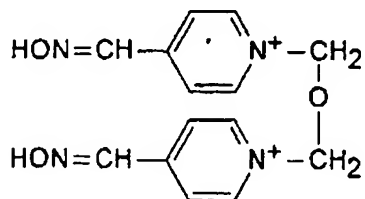
TRADE NAME:	TETRACAIN (ALCON)
CLINICAL USE:	ANAESTHETIC (TOPICAL)

127. TICLOPIDINE [55142-85-3, 53885-31-1(HYDROCHLORIDE)]

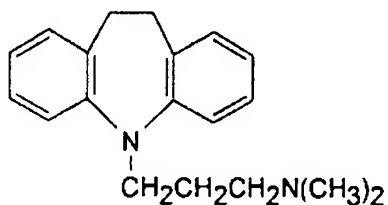
TRADE NAME:	TICLID (SANOFI WINTHROP)
CLINICAL USE:	PLATELET AGGREGATION INHIBITOR

128. TOCAINIDE [41708-72-9]

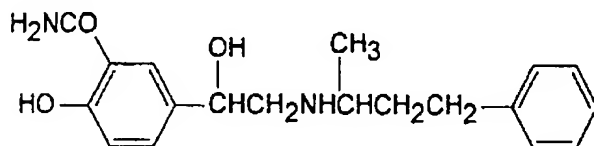
TRADE NAME:	TONOCARD (HÄSSLE)
CLINICAL USE:	ANTIARRHYTHMIC

129. OBIDOXIME CHLORIDE [114-90-9]

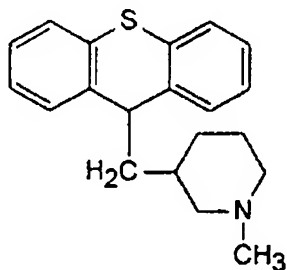
TRADE NAME:	TOXOGONIN (MEDA)
CLINICAL USE:	CHOLINESTERASE REACTIVATOR

130. IMIPRAMINE [50-49-7, 113-52-0(HYDROCHLORIDE)]

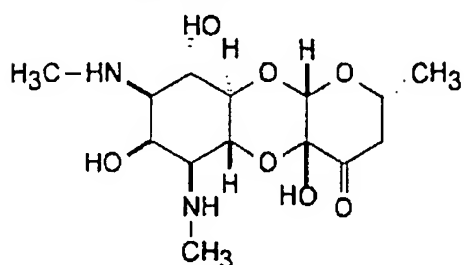
TRADE NAME:	TOFRANAL (CIBA)
CLINICAL USE:	ANTIDEPRESSANT

131. LABETALOL [36894-69-6, 32780-64-6(HYDROCHLORIDE)]

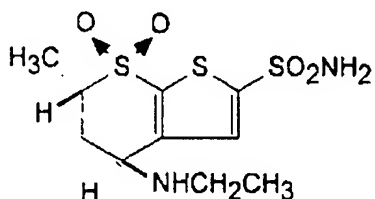
TRADE NAME:	TRANDATE (GLAXO WELLCOME)
CLINICAL USE:	ANTIHYPERTENSIVE

132. METHIZENE [4969-02-2, 7081-4-5(HYDROCHLORIDE)]

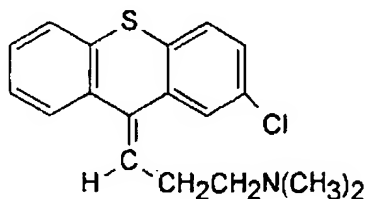
TRADE NAME:	TREMOQUIL (ASTRA)
CLINICAL USE:	ANTICHOLINERGIC ANTIPARKINSON

133. SPECTINOMYCIN [1695-77-8, 22189-32-3(HYDROCHLORIDE)]

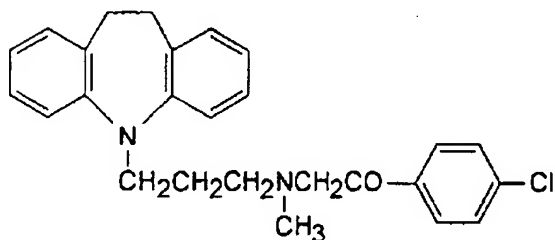
TRADE NAME:	TROBICIN (PHARMACIA & UPJOHN)
CLINICAL USE:	ANTIBIOTIC

134. DORZOLAMIDE []

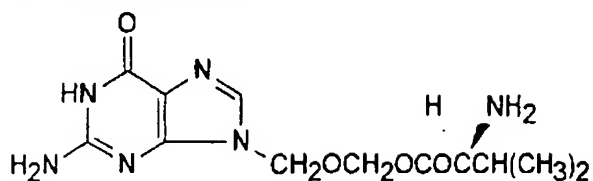
TRADE NAME:	TRUSOPT (MSD)
CLINICAL USE:	ANTIGLAUCOMA, CARBONIC ANHYDRASE ANTAGONIST

135. CHLORPROTHIXENE [113-59-7]

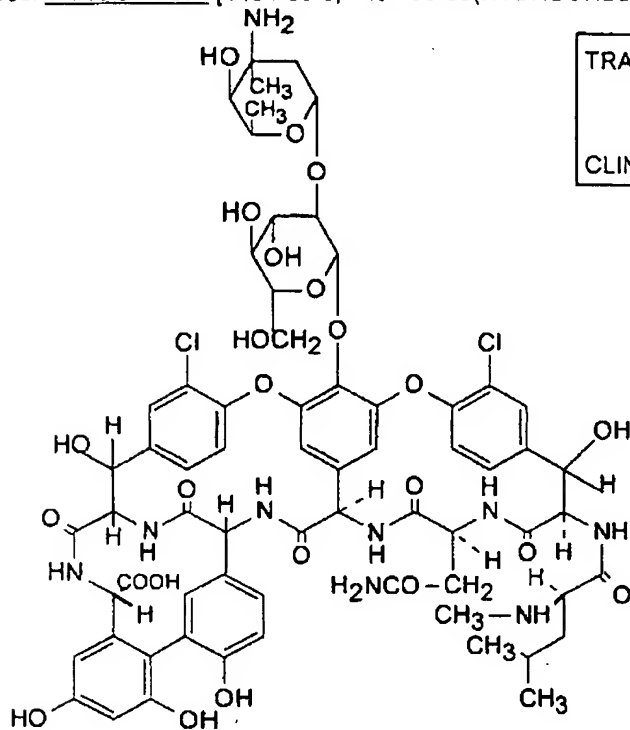
TRADE NAME:	TRUXAL (LUNDBECK)
CLINICAL USE:	ANTIPSYCHOTIC

136. LOFEPRAMINE [23047-25-8, 26786-32-3(HYDROCHLORIDE)]

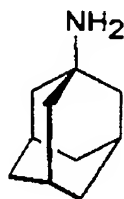
TRADE NAME:	TYMELYT (LUNDBECK)
CLINICAL USE:	ANTIDEPRESSANT

137. VALACIKLOVIR []

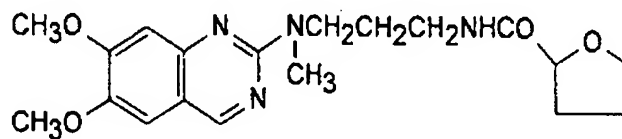
TRADE NAME:	VALTREX (GLAXO WELLCOME)
CLINICAL USE:	ANTIVIRAL AGENT

138. VANCOMYCIN [1404-90-6, 1404-93-09(HYDROCHLORIDE)]

TRADE NAME:	VANCOCIN (LILLY) VANCOMYCIN (DUMEX) VANCOMYCIN (NORCOX)
CLINICAL USE:	ANTIBACTERIAL

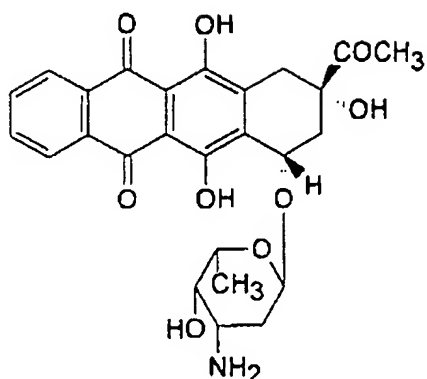
139. AMANTADINE [768-94-5, 665-66-7(HYDROCHLORIDE)]

TRADE NAME:	VIROFRAL (FERROSAN)
CLINICAL USE:	ANTIVIRAL (INFLUENZA A)

140. ALFLUZOSINE []

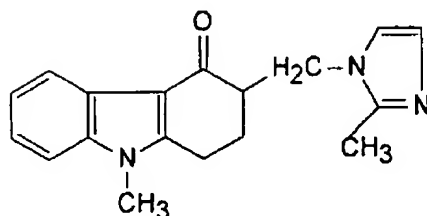
TRADE NAME:	XATRAL (ASTRA)
CLINICAL USE:	α 1-RECEPTOR ANTAGONIST

141. IDARUBICIN []



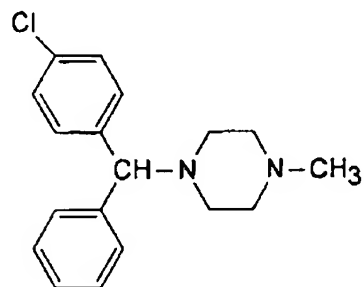
TRADE NAME:	ZAVEDOS (PHARMACIA & UPJOHN)
CLINICAL USE:	CYTOSTATIC

142. ONDANSETRON [99614-02-5, 99614-01-4(HYDROCHLORIDE)]



TRADE NAME:	ZOFRAN (GLAXO WELLCOME)
CLINICAL USE:	ANTIEMETIC

143. CETIRIZINE [83881-51-0, 83881-52-1 (HYDROCHLORIDE)]



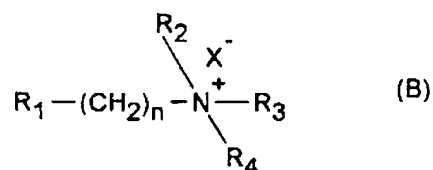
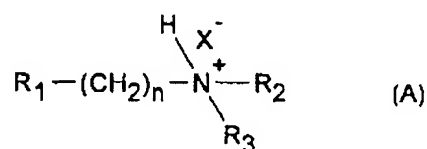
TRADE NAME:	ZYRLEX (UCB)
CLINICAL USE:	ANTIHISTAMINE

It is to be understood that the invention is not limited to the features and embodiments hereinabove specifically set forth, but may be carried out in other ways without departure from its spirit.

CLAIMS

What is claimed is:

1. A method of administering to a human patient material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:



wherein R_1 comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R_2 , R_3 and R_4 and alkyl or aryl groups, and X^- is an anion, said method comprising the steps of

- (a) providing a sterile injectable formulation comprising a liquid vehicle containing the material in solution, at a pH within a range of about 5.5 to 7.0, and

- (b) injecting the formulation into the patient in an amount for delivering to the patient a dose of about one to 100 mg/kg of the material while the pH of the formulation is within said range.

2. A method according to claim 1, wherein said hydrogen bond acceptor site is a carbonyl or carboxylic oxygen atom.

3. A method according to claim 1, wherein X^- is Cl^- , F^- , Br^- or I^- .

4. A method according to claim 1, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.

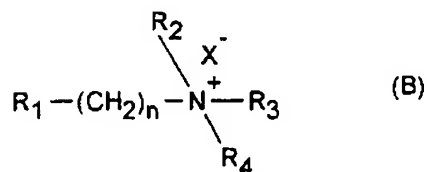
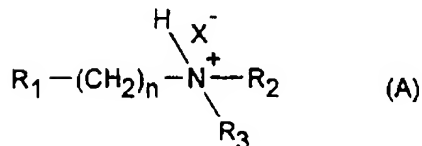
5. A method according to claim 1, wherein said formulation is provided at a concentration of about 100 to 7000 mg/ml.

6. A method according to claim 1, wherein the injecting step comprises injecting the formulation intramuscularly into the patient.

7. A sterile injectable formulation for intramuscular administration to a human patient, comprising

- (a) a material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid

salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:



wherein R_1 comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R_2 , R_3 and R_4 are alkyl or aryl groups, and X^- is an anion;

- (b) a liquid vehicle in which said material is in solution;
- (c) said material being present in said formulation in a concentration of at least about 50 mg/ml, and
- (d) the formulation being at a pH within a range of about 5.5 to 7.0.

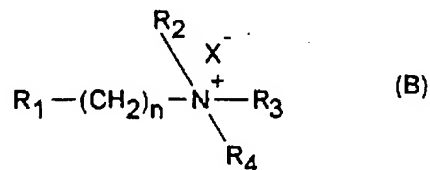
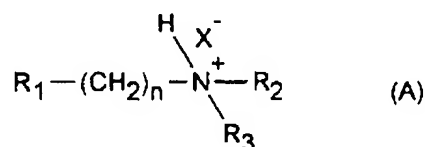
8. A formulation as defined in claim 7, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.

9. A formulation as defined in claim 7, also including an amount of a buffer or preservative effective to stabilize the pH of the formulation.

10. A formulation as defined in claim 9, including an amount of a phosphate buffer effective to stabilize the pH of the formulation to a range of less than 0.5 pH unit.

11. A formulation as defined in claim 9, including an amount of sodium metabisulfite effective to stabilize the pH of the formulation to a range of less than 0.5 pH unit.

12. A method of administering to a human patient material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:



wherein R_1 comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R_2 , R_3 and R_4 are alkyl or aryl groups, and X^- is an anion, said method comprising the steps of

- (a) providing a sterile formulation, comprising a liquid vehicle containing the material in solution,
- (b) adjusting the pH of said formulation for reducing the development of undesirable side effects of the material, and
- (c) administering the formulation having the adjusted pH to the patient.

13. A method according to claim 12, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.

14. A method of administering to a human patient material selected from the group consisting of acid addition salts of malphalan, amiloride, clomipramine, chlorcyclizine, hydralazine, alprenolol, dopamine, quinapril, tetracycline, cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine, chlortetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine, phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem, clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine, ethylmorphine, tacrine, protriptyline, amiodarone, cyclopentolate, clindamycin, propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine, doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin,

flupentixol, benoxinate, fluoxetin, gemcitabine, adrenaline, metformin, chloropromazine, prenalterol, terazosine, oxymetazoline, loperamide, propranolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine, ketamine, ketobemidon, quinidine, granisetron, mefloquin, promethazine, remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benserazide, thioridazine, cyclizine, cephepime, methadone, mexiletine, mianserin, pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium, naloxone, xylometazoline, procarbazine, tropisetron, phenylephrine, thiamine, tramadol, hydrochlorotiazid, quinagolide, noscapine, mitoxantrone, dipivefrin, oxytetracycline, fluphenazine, chlorguanide, trihexyphenidyl, bacampicillin, cyproheptadine, prazosin, meperidine, meclizine, metoclopramide, procainamide, pyridoxine, alfentanil, naphazoline, methacycline, roxatidine, propafenone, amitriptyline, nortriptyline, paroxetine, clobutinol, sotalol, buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine, labetalol, methixene, spectinomycin, dorzolamide, chloroprophixene, lefepramine, valaciclovir, vancomycin, amantadine, alfluzosine, idarubicin, ondansetron, cetirizine, 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline and mixtures thereof, said method comprising the steps of

- (a) providing a sterile injectable formulation comprising a liquid vehicle containing the material in solution, at a pH within a range of about 5.5 to 7.0, and
- (b) injecting the formulation into the patient in an amount for delivering to the patient a dose of about one to 100 mg/kg of the material while the pH of the formulation is within said range.

15. A method according to claim 14, wherein the injecting step comprises injecting the formulation intramuscularly into the patient.

16. A sterile injectable formulation for intramuscular administration to a human patient, comprising

- (a) a material selected from the group consisting of acid addition salts of malphalan, amiloride, clomipramine, chlorcyclizine, hydralazine, alprenolol, dopamine, quinapril, tetracycline, cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine, chlortetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine, phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem, clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine, ethylmorphine, tacrine, protriptyline, amiodarone, cyclopentolate, clindamycin, propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine, doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin, flupentixol, benoxinate, fluoxetine, gemcitabine, adrenaline, metformin, chlorpromazine, prenalterol, terazosine, oxymetazoline, loperamide, propranolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine, ketamine, ketobemidon, quinidine, granisetron, mefloquin, promethazine, remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benserazide, thioridazine, cyclizine, cephepime, methadone, mexiletine, mianserin, pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium, naloxone, xylometazoline, procarbazine, tropisetron, phenylephrine; thiamine, tramadol, hydrochlorothiazide, quinagolide, noscapine, mitoxantrone, dipivefrin, oxytetracycline, fluphenazine,

- chlorguanide, trihexyphenidyl, bacampicillin, cyproheptadine, prazosin, meperidine, meclizine, metoclopramide, procainamide, pyridoxine, alfentanil, naphazoline, methacycline, roxatidine, propafenone, amitriptyline, nortriptyline, paroxetine, clobutinol, sotalol, buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine, labetalol, methixene, spectinomycin, dorzolamide, chlorprothixene, lefepramine, valaciclovir, vancomycin, amantadine, alfluzosine, idarubicin, ondansetron, cetirizine, 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl-(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline and mixtures thereof.
- (b) a liquid vehicle in which said material is in solution,
 - (c) said material being present in said formulation in a concentration of at least about 50 mg/ml, and
 - (d) the formulation being at a pH within a range of about 5.5 to 7.0.

17. A method of administering to a human patient material selected from the group consisting of acid addition salts of malphalan, amiloride, clomipramine, chlorcyclizine, hydralazine, alprenolol, dopamine, quinapril, tetracycline, cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine, chlortetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine, phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem, clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine, ethylmorphine, tacrine, protriptyline, amiodarone, cyclopentolate, clindamycin, propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine, doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin, flupentixol, benoxinate, fluoxetine, gemcitabine, adrenaline, metformin,

chloropromazine, prenalterol, terazosine, oxymetazoline, loperamide, propanolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine, ketamine, ketobemidon, quinidine, granisetron, mefloquin, promethazine, remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benserazide, thioridazine, cyclizine, cephepime, methadone, mexiletine, mianserin, pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium, naloxone, xylometazoline, procarbazine, tropisetron, phenylephrine, thiamine, tramadol, hydrochlorotiazid, quinagolide, noscapine, mitoxantrone, dipivefrin, oxytetracycline, fluphenazine, chlorguanide, trihexyphenidyl, bacampicillin, cyproheptadine, prazosin, meperidine, meclizine, metoclopramide, procainamide, pyridoxine, alfentanil, naphazoline, methacycline, roxatidine, propafenone, amitriptyline, nortriptyline, paroxetine, clobutinol, sotalol, buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine, labetalol, methixene, spectinomycin, dorzolamide, chloroprothixene, lefepramine, valaciclovir, vancomycin, amantadine, alfluzosine, idarubicin, ondansetron, cetirizine, 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline and mixtures thereof

- (a) providing a sterile formulation, comprising a liquid vehicle containing the material in solution,
- (b) adjusting the pH of said formulation for reducing the development of undesirable side effects of the material, and
- (c) administering the formulation having the adjusted pH to the patient.

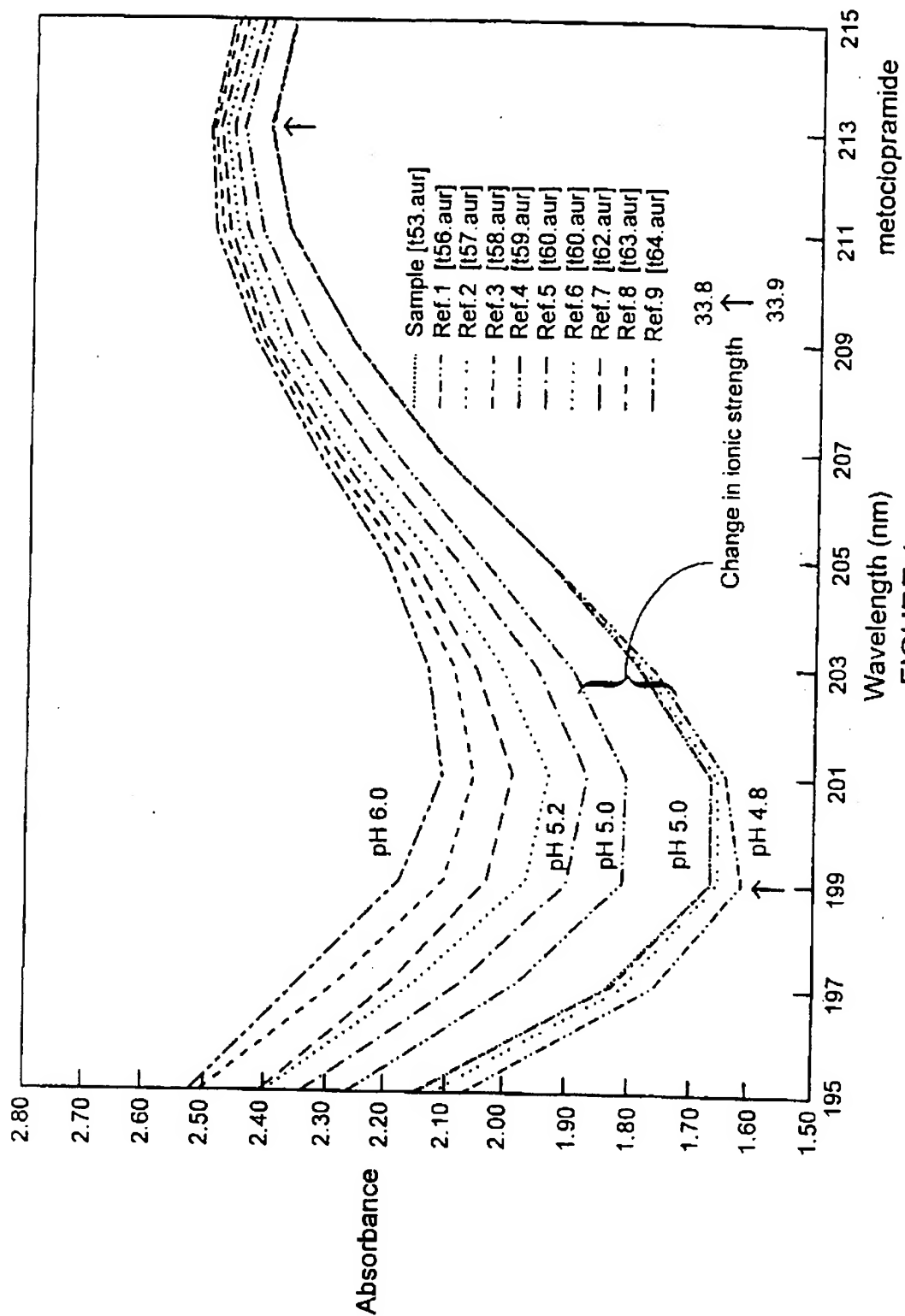


FIGURE 1

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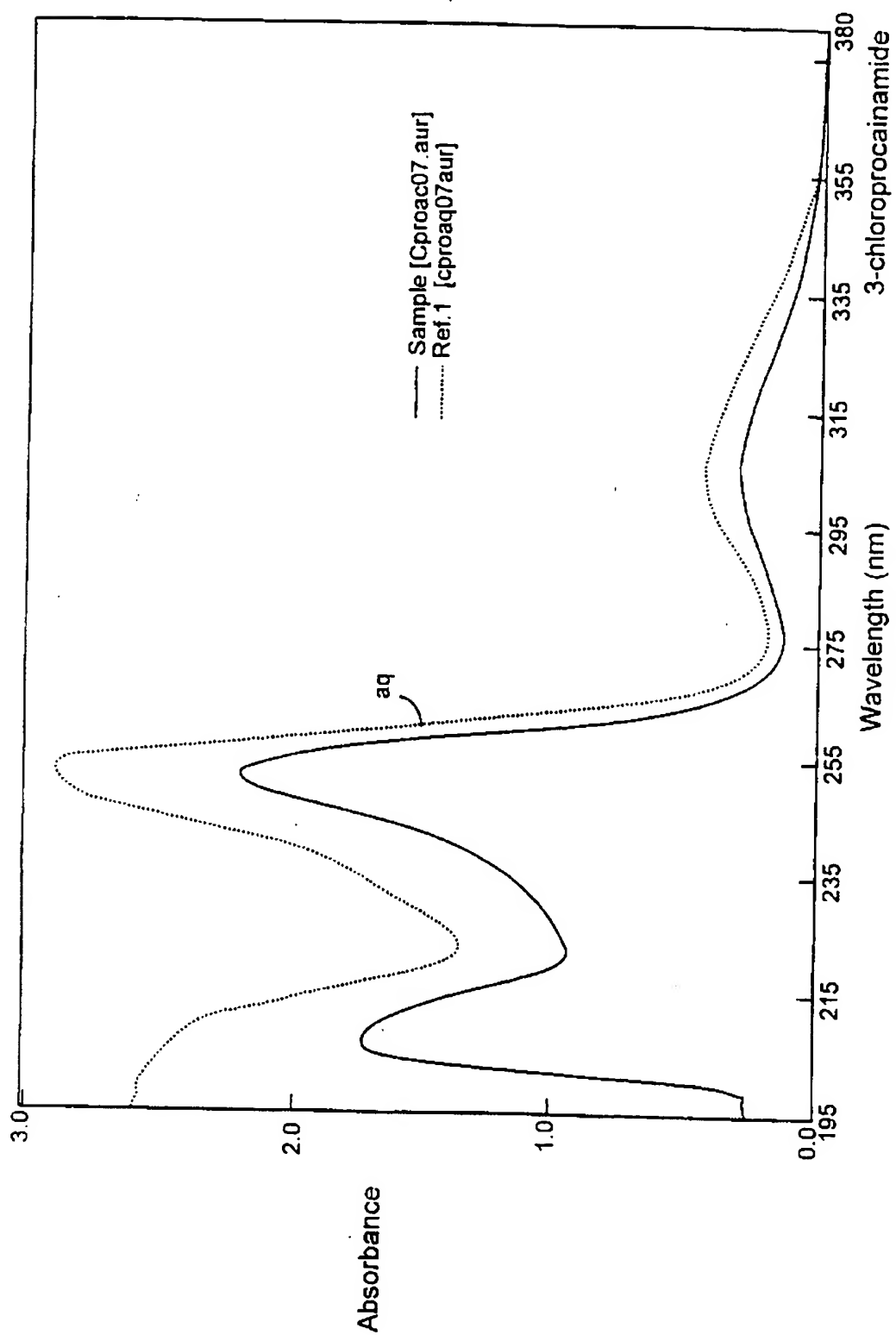


FIGURE 2A

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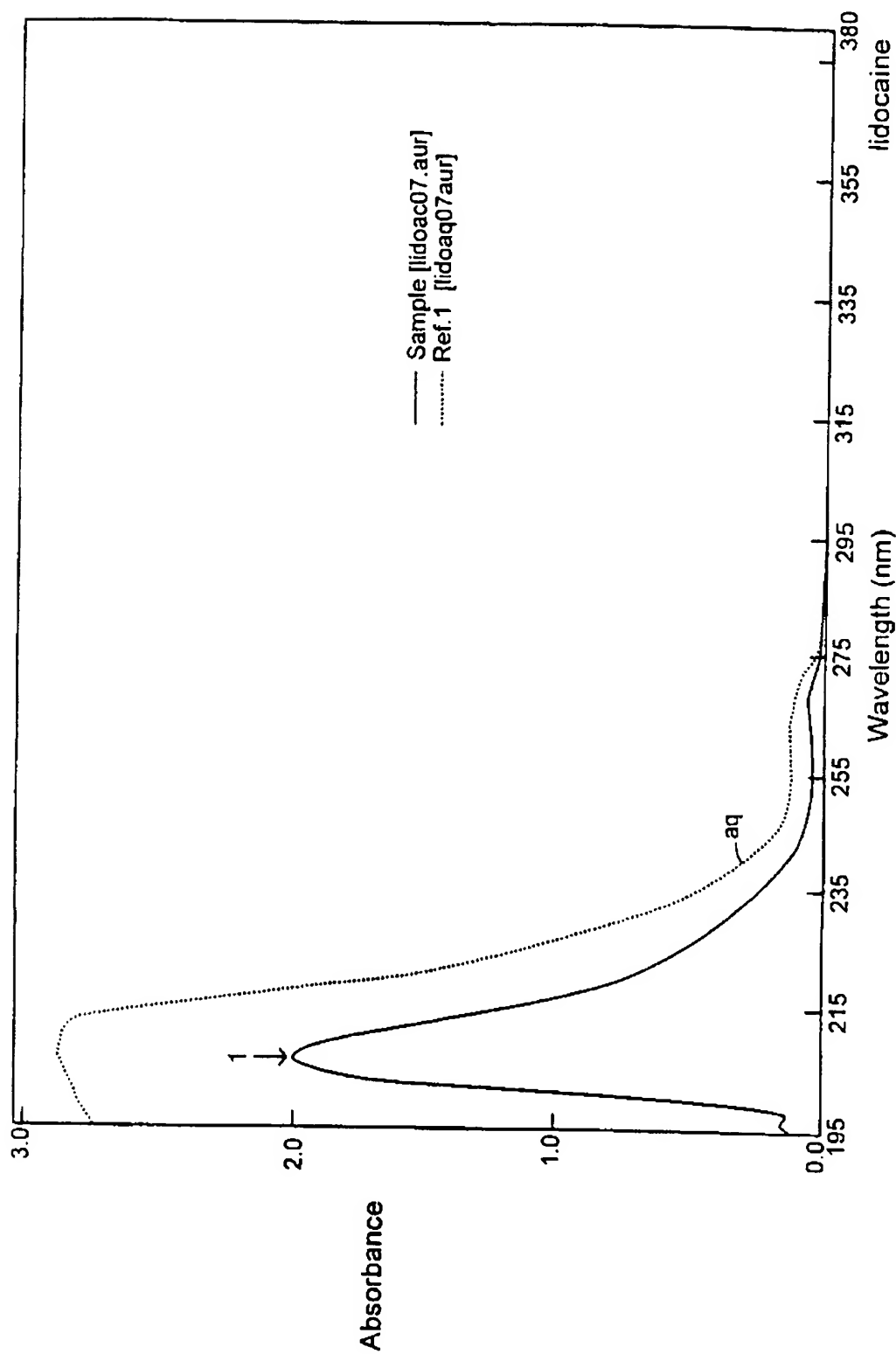


FIGURE 2B

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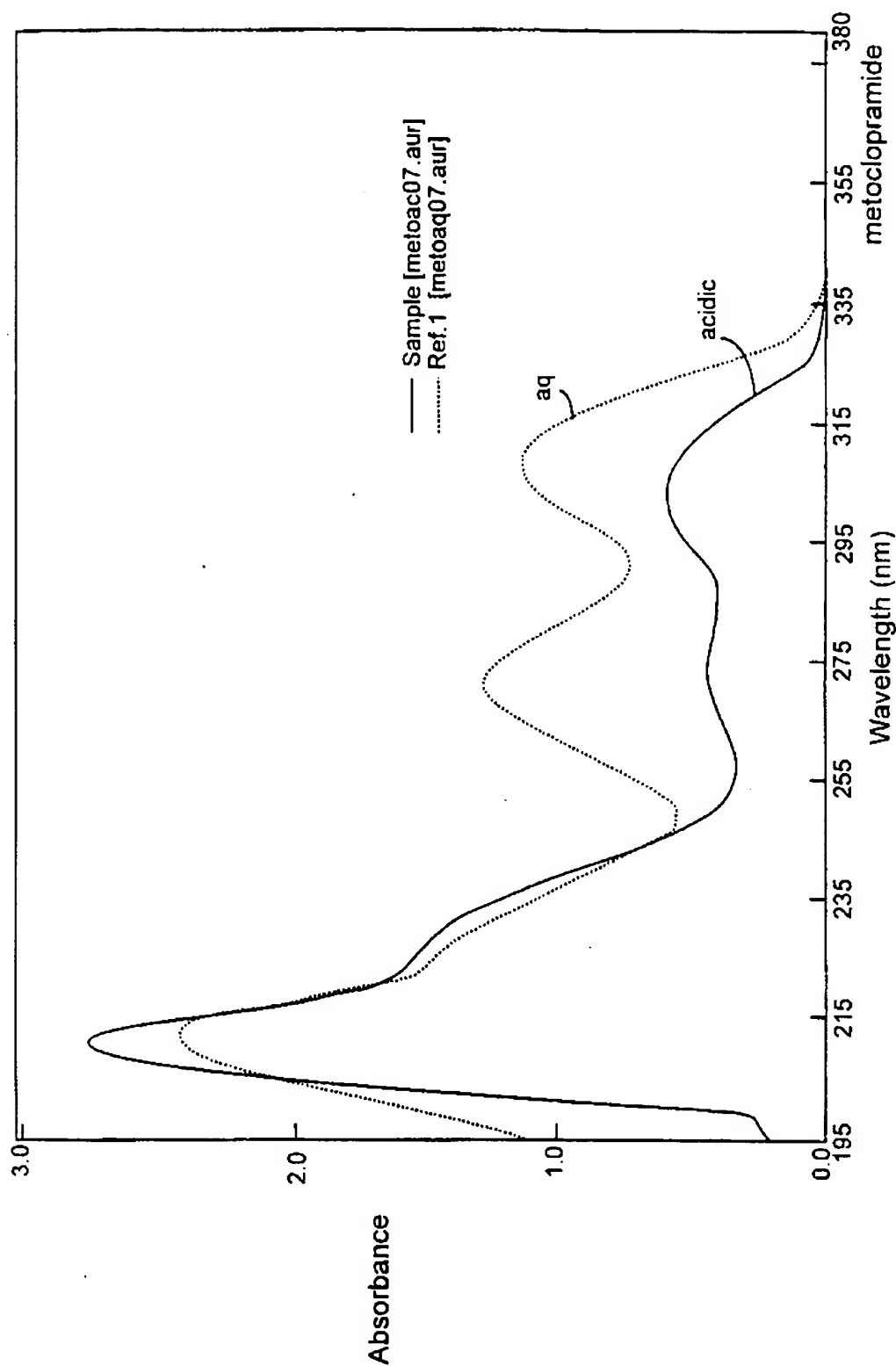


FIGURE 2C

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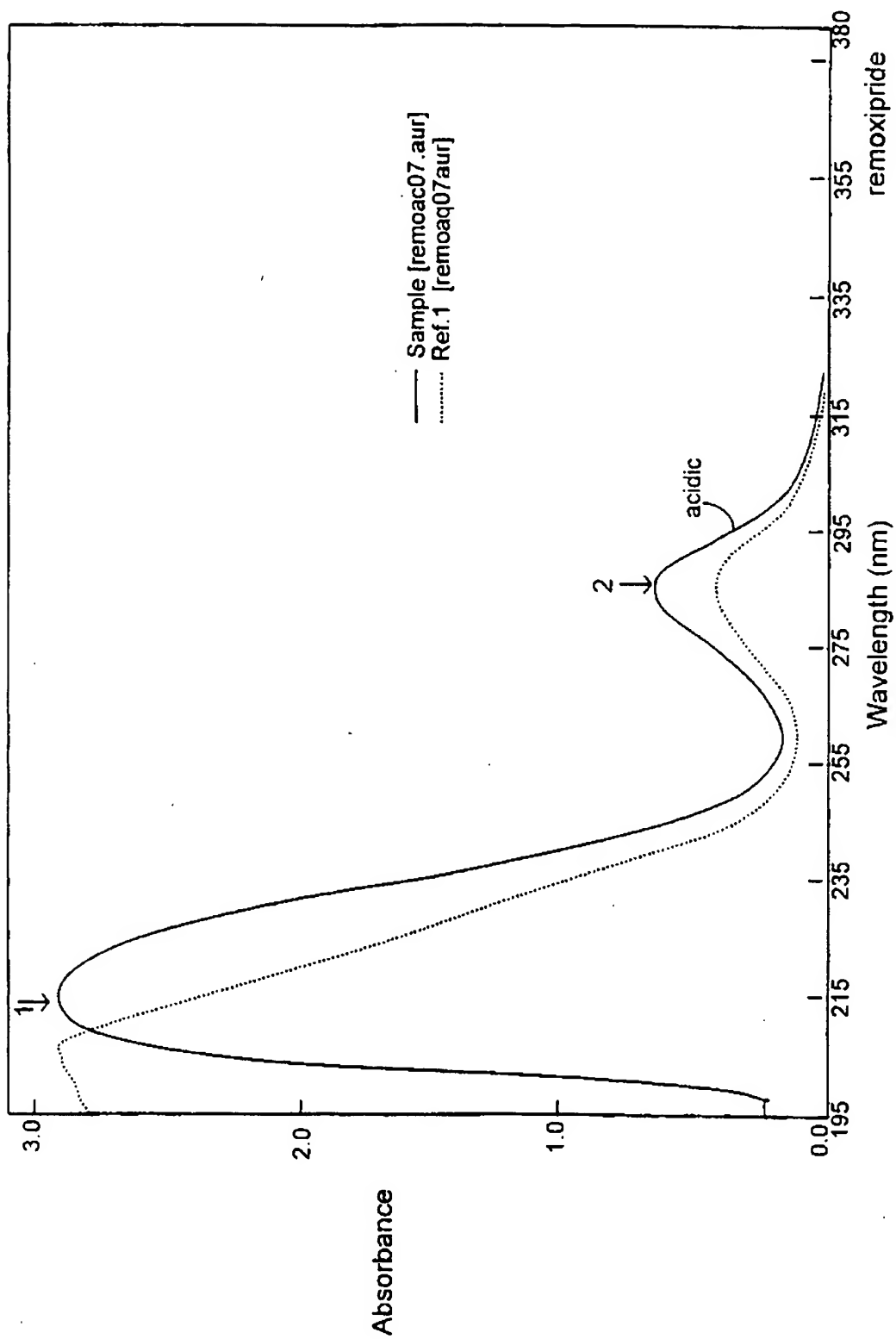


FIGURE 2D

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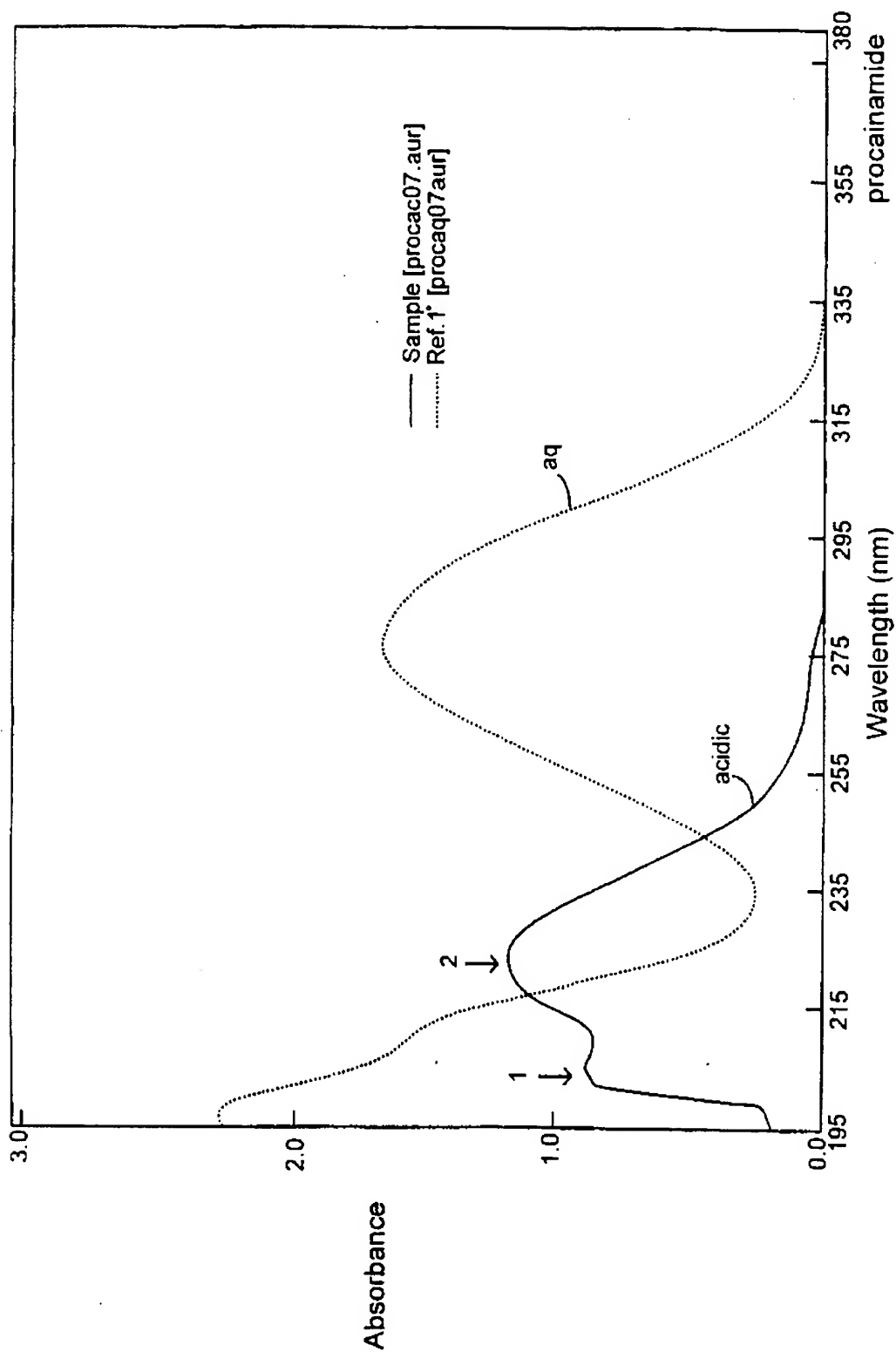


FIGURE 2E

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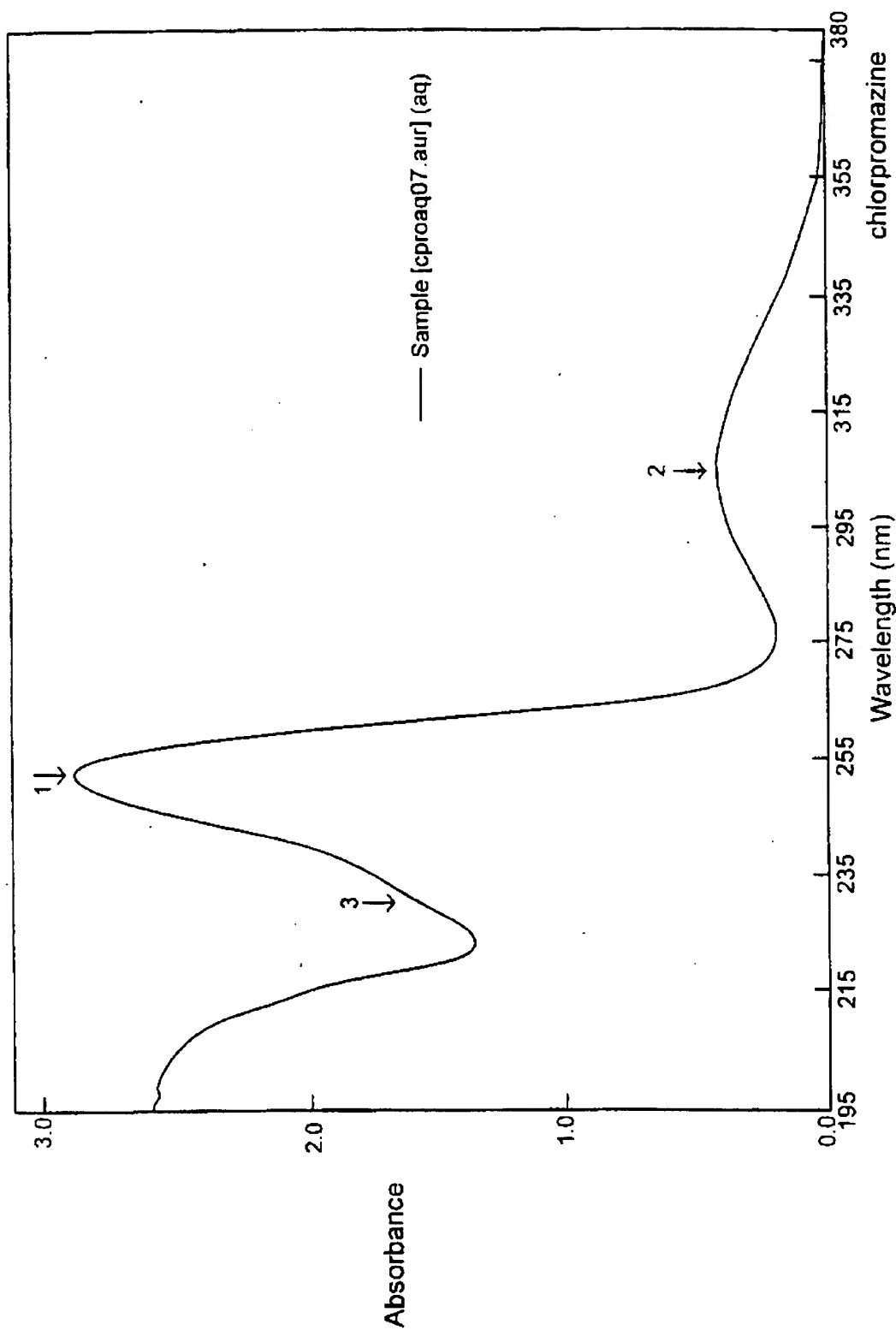


FIGURE 2F

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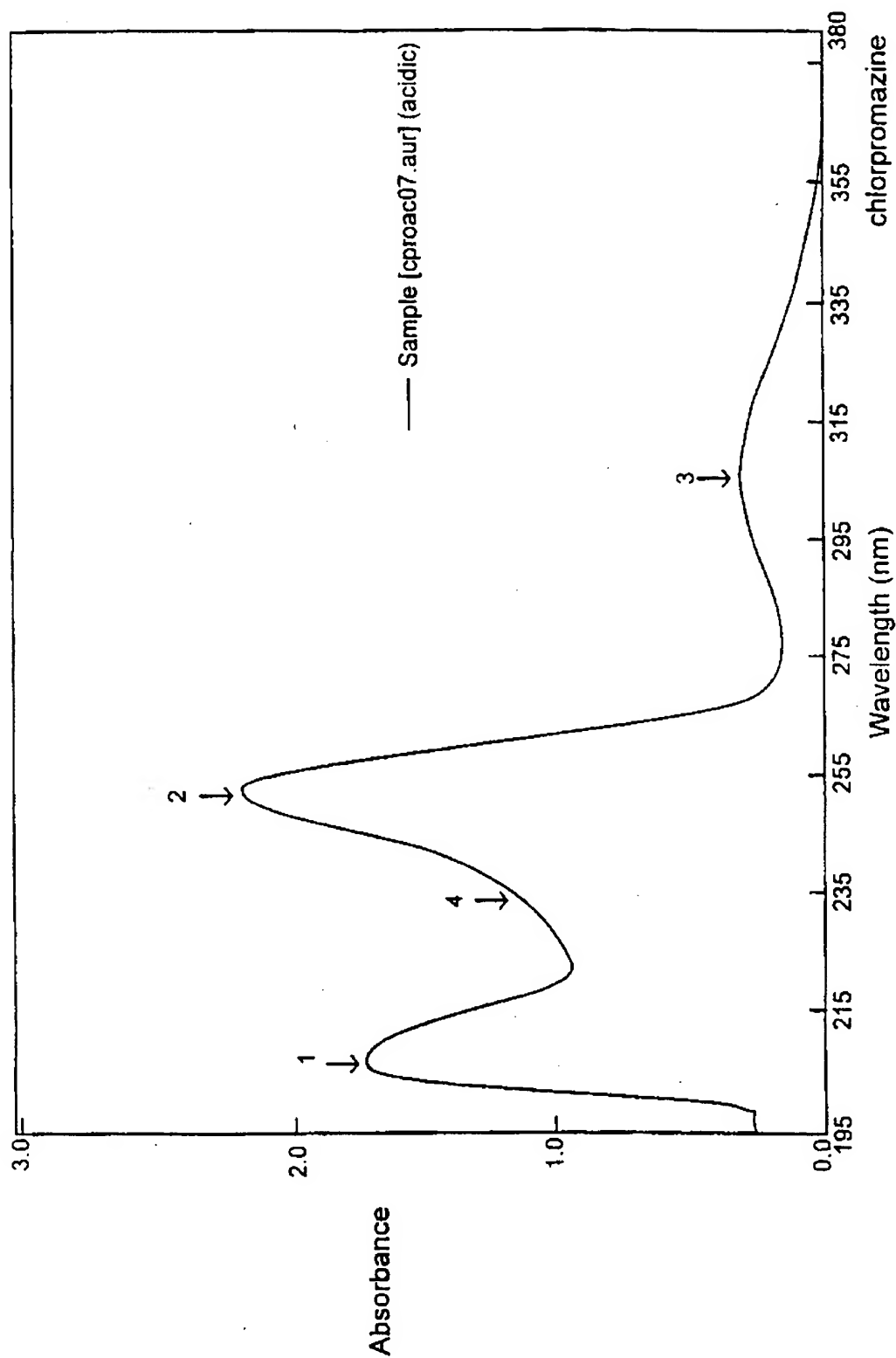


FIGURE 2G

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10829

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A61K 38/16, 31/13, 31/135, 31/14, 31/155, 31/16, 31/165, 31/18 US CL : Please See Extra Sheet. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : Please See Extra Sheet. Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ON-LINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,536,386 A (KEENAN) 20 August 1985, see entire document.	1-13
Y	US 5,260,289 (HYODO ET AL.) 09 November 1993, see entire document.	14-17
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* documents defining the general state of the art which is not considered to be of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family		
Date of the actual completion of the international search 06 AUGUST 1997		Date of mailing of the international search report 03 SEP 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Phyllis Spivack</i> PHYLLIS SPIVACK Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10829

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/8, 24, 25, 34, 152, 210, 211, 217, 223.2, 225.5, 225.8, 31/195, 31/215, 31/22, 31/225, 31/275, 31/335, 31/34, 31/38, 31/40, 31/415, 31/44, 31/445, 31/47, 31/395, 31/495, 31/505, 31/51, 31/52, 31/535, 31/54, 31/55, 31/65, 31/70, 226.2, 239.5, 248, 250, 255, 260, 262, 276, 289, 290, 291, 297, 299, 304, 307, 312, 314, 317, 321., 324, 325, 326, 327, 330, 331, 332, 338, 345, 397, 400, 401, 428, 432, 437, 452, 469, 471, 523, 530, 535, 546, 547, 567, 605, 614, 615, 619, 620, 626, 635, 643, 646-648, 651-6, 659, 662, 669

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/8, 24, 25, 34, 152, 210, 211, 217, 223.2, 225.5, 225.8, 31/195, 31/215, 31/22, 31/225, 31/275, 31/335, 31/34, 31/38, 31/40, 31/415, 31/44, 31/445, 31/47, 31/395, 31/495, 31/505, 31/51, 31/52, 31/535, 31/54, 31/55, 31/65, 31/70, 226.2, 239.5, 248, 250, 255, 260, 262, 276, 289, 290, 291, 297, 299, 304, 307, 312, 314, 317, 321., 324, 325, 326, 327, 330, 331, 332, 338, 345, 397, 400, 401, 428, 432, 437, 452, 469, 471, 523, 530, 535, 546, 547, 567, 605, 614, 615, 619, 620, 626, 635, 643, 646-648, 651-6, 659, 662, 669